

Supporting Information

One-pot Ugi-azide and Heck reactions for the synthesis of heterocyclic systems containing tetrazole and 1,2,3,4-tetrahydroisoquinoline

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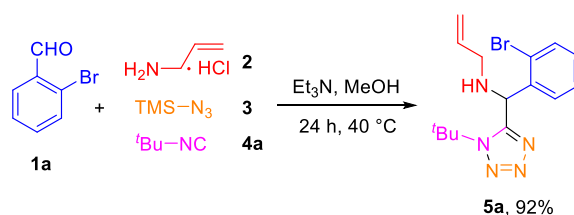
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1. General Information

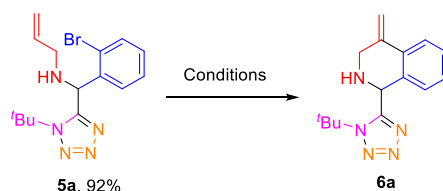
Chemicals and solvents were purchased from commercial sources and used without further purification. ^1H (300MHz, 400 MHz), ^{13}C NMR spectra (75 MHz or 126 MHz) were recorded on a Bruker NMR spectrometer. LC-MS were performed on an Agilent 2100 system with C_{18} column (5.0 μm , 6.0 x 50 mm). The mobile phases were MeOH and H_2O both containing 0.05% trifluoroacetic acid. A linear gradient was used to increase from 25:75 (v/v) MeOH/ H_2O to 100% MeOH in 7.0 min at a flow rate of 0.7 mL/min. UV detections were conducted at 210 nm, 254 nm and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). HRMS were performed on Agilent 6540 Q-TOF mass spectrometer (ESI). Flash column chromatography was performed using silica gel (200-300 mesh).

2. General procedure for the synthesis of Ugi-azide adducts 5a



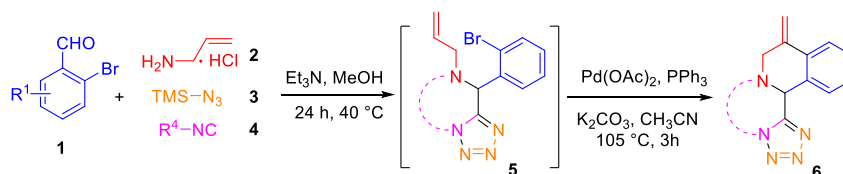
A solution of 2-bromobenzaldehyde **1** (1 mmol, 1 equiv), allylamine hydrochloride **2** (1 mmol, 1 equiv), trimethylsilyl azide **3** (1 mmol, 1 equiv) and *tert*-butyl isocyanide **4a** (1 mmol, 1 equiv) in MeOH (5 mL) with Et_3N (1.5 mmol) was heated at $40\text{ }^\circ\text{C}$ for 12 h in a sealed vial. Upon the reaction completed, the reaction mixture was filtered, then evaporating under vacuum to give crude products **5a**. Further purification was conducted by flash chromatography with 1: 6 petroleum ether/EtOAc to afford **5a** in 92% yields. The adduct was confirmed and NMR. This is a typical procedure for the Ugi-azide step in this paper.

3. General procedure of Heck reaction for the synthesis of product 6a



To a solution of Ugi-azide adduct **5a** (0.1 mmol) with $\text{Pd}(\text{OAc})_2$ (0.1 mmol), PPh_3 (0.2 mmol), K_2CO_3 (2 mmol) or NaOAc (2 mmol) in MeCN (3 mL) at $105\text{ }^\circ\text{C}$ for 3 h under nitrogen atmosphere. After aqueous work up, the crude product was purified by flash chromatography with 1:4 ethyl acetate/petroleum ether to afford product **6a**.

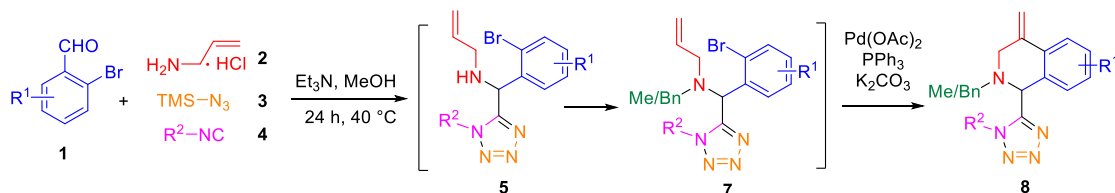
4. General procedure for the one-pot synthesis of tetrazole-containing 1,2,3,4-tetrahydroisoquinolines 6



A mixture of 2-bromobenzaldehyde **1** (1 mmol), allylamine hydrochloride **2** (1 mmol), trimethylsilyl azide **3** (1 mmol) and isocyanide **4** (1 mmol) was stirred in MeOH at $40\text{ }^\circ\text{C}$ for 24 h, after the reaction was completed, the

solvent was evaporated under vacuum to give crude Ugi adduct **5**, without further purification, the crude intermediate **5** in MeCN (3 mL) was used for the Heck reaction with 10 mol% of Pd(OAc)₂, 20 mol% of PPh₃, 2 equiv of K₂CO₃ for 3 h at 105 °C under N₂ atmosphere. After aqueous work up, the crude product was purified by flash chromatography with 1:3 ethyl acetate/petroleum ether to afford product **6**.

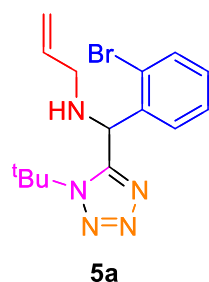
5. General procedure for the one-pot synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinolines **8**



A mixture of 2-bromobenzaldehyde **1** (1 mmol), allylamine hydrochloride **2** (1 mmol), trimethylsilyl azide **3** (1 mmol) and isocyanide **4** (1 mmol) in MeOH was reacted at 40 °C for 24 h. After evaporating the solvent, 3 mL CH₃CN was added to the crude 1,5-DS-1*H*-T **5** followed by the addition of 1 equiv of benzyl bromide or iodomethane and 2 equiv of K₂CO₃ for the alkylation reaction at 80 °C for 3 h to give *N*-alkylated compounds **7**. Finally, 10 mol% of Pd(OAc)₂, 20 mol% of PPh₃, 2 equiv of K₂CO₃ were added to the reaction mixture for the Heck reaction at 105 °C for 3 h under N₂ atmosphere, after aqueous work up, the crude product was purified by flash chromatography with 1:3 ethyl acetate/petroleum ether to afford product **8**.

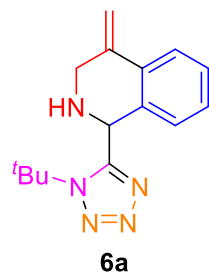
6. Analytical data of products

N-((2-bromophenyl)(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)methyl)prop-2-en-1-amine (**5a**)



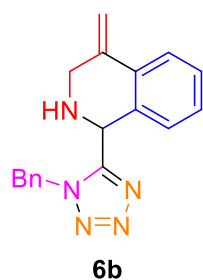
White solid, 321mg, 92% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.08 (dd, *J* = 7.6, 1.8 Hz, 1H), 5.94 (dddd, *J* = 18.4, 9.5, 7.2, 5.4 Hz, 1H), 5.72 (s, 1H), 5.10 (t, *J* = 1.5 Hz, 1H), 5.07 (dd, *J* = 6.2, 1.6 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.19 – 3.12 (m, 1H), 2.36 (s, 1H), 1.57 (s, 9H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 154.7, 138.2, 136.0, 133.6, 130.0, 129.0, 128.3, 124.3, 117.6, 61.6, 56.2, 50.9, 29.8. HRMS (ESI) calcd for C₁₅H₂₀BrN₅ ([M+Na]⁺): 372.0800, found 372.0792.

1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-4-methylene-1,2,3,4-tetrahydroisoquinoline (**6a**)



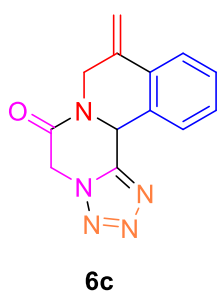
Light yellow oil, 161mg, 60% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.73 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 1.3 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 5.74 (s, 1H), 5.61 (s, 1H), 5.04 (s, 1H), 3.80 (d, *J* = 15.2 Hz, 1H), 3.68 (s, 1H), 2.03 (d, *J* = 16.7 Hz, 1H), 1.85 (s, 9H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 155.5, 138.8, 133.9, 133.0, 128.2, 128.0, 126.7, 124.5, 108.3, 62.1, 53.1, 48.6, 30.2. HRMS (ESI) calcd for C₁₅H₁₉N₅ ([M+Na]⁺): 292.1538, found 292.1520.

1-(1-benzyl-1H-tetrazol-5-yl)-4-methylene-1,2,3,4-tetrahydroisoquinoline (6b)



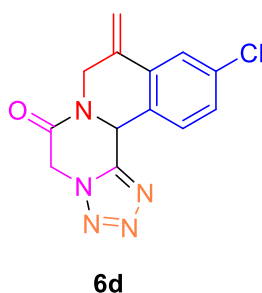
yellow oil, 174 mg, 58 yield. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.67 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.21 (dd, $J = 5.2, 2.2$ Hz, 4H), 7.09 – 7.03 (m, 2H), 6.99 (td, $J = 7.6, 1.3$ Hz, 1H), 6.52 (d, $J = 7.8$ Hz, 1H), 5.66 – 5.55 (m, 3H), 5.48 (d, $J = 14.9$ Hz, 1H), 5.04 (d, $J = 1.4$ Hz, 1H), 3.68 – 3.54 (m, 2H), 2.47 (s, 1H). ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 150.4, 133.5, 128.5, 127.6, 126.9, 123.5, 123.2, 123.0, 122.9, 122.7, 121.9, 119., 103.2, 72.4, 72.1, 71.8, 47.1, 46.2, 43.6. HRMS (ESI) calcd for C₁₈H₁₇N₅ ([M+Na]⁺): 326.1832, found 326.1817.

9-methylene-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (6c)



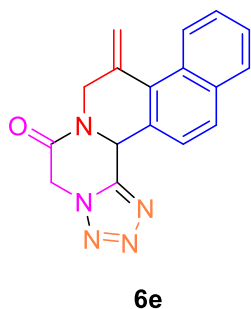
Light yellow solid, 192 mg, 76% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.34 (dt, $J = 15.8, 7.3$ Hz, 2H), 6.33 (s, 1H), 5.75 (s, 1H), 5.43 (d, $J = 15.0$ Hz, 1H), 5.34 (s, 1H), 5.20 (d, $J = 18.0$ Hz, 1H), 4.98 (d, $J = 18.0$ Hz, 1H), 3.91 (d, $J = 15.0$ Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.5, 147.9, 135.5, 132.57, 129.8, 129.2, 129.0, 125.9, 124.9, 112.0, 53.7, 48.0, 47.8. HRMS (ESI) calcd for C₁₃H₁₁N₅O ([M+Na]⁺): 276.0866, found 276.0861.

11-chloro-9-methylene-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (6d)



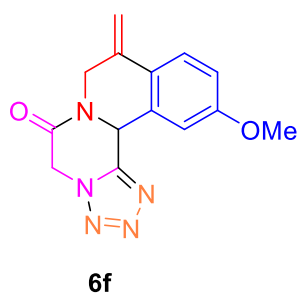
White solid, 215 mg, 75% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, $J = 8.5$ Hz, 1H), 7.68 (d, $J = 1.9$ Hz, 1H), 7.31 (dd, $J = 8.5, 1.9$ Hz, 1H), 6.31 (s, 1H), 5.77 (s, 1H), 5.45 (d, $J = 15.1$ Hz, 1H), 5.42 (s, 1H), 5.24 (d, $J = 18.0$ Hz, 1H), 5.03 (d, $J = 18.0$ Hz, 1H), 3.90 (d, $J = 15.0$ Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.4, 147.7, 135.4, 134.5, 134.3, 129.0, 128.1, 127.6, 124.9, 113.3, 53.3, 47.8, 47.6. HRMS (ESI) calcd for C₁₃H₁₀ClN₅O ([M+Na]⁺): 310.0472, found 310.0472.

*9-methylene-9,15b-dihydro-8H-benzo[*g*]tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (6e)*



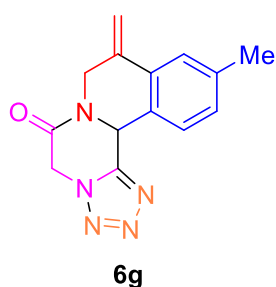
Light yellow solid, 230 mg, 76% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.38 (d, $J = 8.0$ Hz, 1H), 7.91 – 7.85 (m, 1H), 7.78 (d, $J = 8.6$ Hz, 1H), 7.62 – 7.52 (m, 2H), 7.34 (d, $J = 8.6$ Hz, 1H), 6.15 (s, 1H), 5.89 (s, 1H), 5.75 (d, $J = 1.9$ Hz, 1H), 5.24 (d, $J = 17.9$ Hz, 1H), 5.01 (dd, $J = 16.5, 7.9$ Hz, 2H), 4.30 (d, $J = 15.0$ Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.2, 147.3, 134.9, 134.1, 132.9, 130.0, 129.5, 128.8, 128.7, 127.5, 126.9, 124.9, 120.6, 120.2, 52.6, 50.0, 47.8. HRMS (ESI) calcd for C₁₇H₁₃N₅O ([M+Na]⁺): 326.1011, found 326.1018.

12-methoxy-9-methylene-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (**6f**)



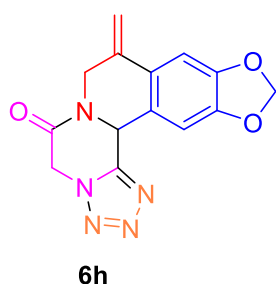
yellow solid, 206 mg, 73% yield. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.28 (s, 1H), 5.58 (d, *J* = 1.5 Hz, 1H), 5.38 (d, *J* = 14.9 Hz, 1H), 5.19 (s, 1H), 5.18 – 5.13 (m, 1H), 4.97 (dd, *J* = 17.9, 1.4 Hz, 1H), 3.85 (d, *J* = 14.9 Hz, 1H), 3.77 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 160.0, 159.4, 147.9, 135.0, 131.0, 126.3, 124.9, 115.7, 110.3, 109.5, 55.5, 53.8, 48.1, 47.7. HRMS (ESI) calcd for C₁₄H₁₃N₅O₂ ([M+Na]⁺): 306.0979, found 306.0967.

11-methyl-9-methylene-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (**6g**)



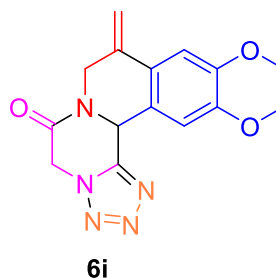
brown solid, 202 mg, 76% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.51 (s, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.29 (s, 1H), 5.74 (s, 1H), 5.42 (d, *J* = 15.0 Hz, 1H), 5.32 (s, 1H), 5.20 (d, *J* = 18.0 Hz, 1H), 4.97 (d, *J* = 17.9 Hz, 1H), 3.89 (d, *J* = 15.0 Hz, 1H), 2.35 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 159.5, 148.1, 139.1, 135.6, 132.3, 129.8, 127.0, 125.8, 125.3, 111.7, 53.6, 48.1, 47.8, 21.2. HRMS (ESI) calcd for C₁₄H₁₃N₅O ([M+Na]⁺): 290.1023, found 290.1018.

9-methylene-9,14b-dihydro-8H-[1,3]dioxolo[4,5-g]tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (**6h**)



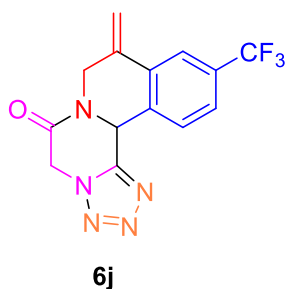
brown solid, 225 mg, 76% yield. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.28 (s, 1H), 7.10 (s, 1H), 6.24 (s, 1H), 5.99 (d, *J* = 1.1 Hz, 1H), 5.94 (d, *J* = 1.1 Hz, 1H), 5.55 (d, *J* = 1.3 Hz, 1H), 5.39 (d, *J* = 14.9 Hz, 1H), 5.24 (s, 1H), 5.20 (d, *J* = 18.1 Hz, 1H), 4.99 (dd, *J* = 18.0, 1.3 Hz, 1H), 3.84 (d, *J* = 14.9 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 159.5, 148.5, 148.5, 148.0, 135.3, 127.0, 123.9, 110.4, 106.1, 104.5, 101.8, 53.6, 47.9, 47.7. HRMS (ESI) calcd for C₁₄H₁₁N₅O₃ ([M+Na]⁺): 320.0753, found 320.0760.

11,12-dimethoxy-9-methylene-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (**6i**)



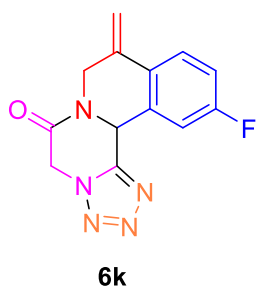
brown solid, 247 mg, 79% yield. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.40 (s, 1H), 7.11 (s, 1H), 6.31 (s, 1H), 5.59 (d, *J* = 1.5 Hz, 1H), 5.43 (d, *J* = 14.8 Hz, 1H), 5.25 (s, 1H), 5.23 – 5.18 (m, 1H), 5.02 (dd, *J* = 18.0, 1.4 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (d, *J* = 14.8 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 159.4, 149.9, 149.4, 148.2, 135.2, 125.0, 122.4, 109.5, 108.4, 106.8, 56.1, 56.0, 53.6, 48.1, 47.7. HRMS (ESI) calcd for C₁₅H₁₅N₅O₃ ([M+Na]⁺): 336.1069, found 336.1069.

9-methylene-11-(trifluoromethyl)-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (**6j**)



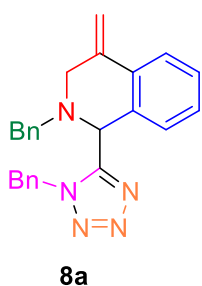
White solid, 237 mg, 74% yield. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 6.38 (s, 1H), 5.86 (s, 1H), 5.53 – 5.48 (m, 2H), 5.26 (d, *J* = 18.4 Hz, 1H), 5.04 (dd, *J* = 18.1, 1.2 Hz, 1H), 3.93 (d, *J* = 15.0 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 159.4, 147.5, 134.4, 133.5, 133.1, 131.8, 131.6, 127.0, 125.5, 121.9, 113.9, 53.5, 47.8, 47.7. ¹⁹F NMR (282 MHz, Chloroform-*d*) δ -63.0. HRMS (ESI) calcd for C₁₄H₁₀F₃N₅O ([M+Na]⁺): 344.0759, found 344.0735.

12-fluoro-9-methylene-9,13b-dihydro-8H-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5H)-one (**6k**)



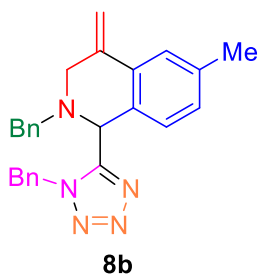
Light yellow solid, 208 mg, 77% yield. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.70 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.59 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.08 (td, *J* = 8.4, 2.6 Hz, 1H), 6.32 (s, 1H), 5.69 (s, 1H), 5.45 (d, *J* = 15.0 Hz, 1H), 5.34 (s, 1H), 5.24 (d, *J* = 18.0 Hz, 1H), 5.06 – 4.99 (m, 1H), 3.90 (d, *J* = 15.0 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 163.6, 161.6, 159.4, 147.6, 134.5, 131.7, 128.7, 127.0, 127.0, 116.7, 116.6, 113.4, 113.2, 111.8, 53.5, 47.9, 47.8. ¹⁹F NMR (282 MHz, Chloroform-*d*) δ -109.9. HRMS (ESI) calcd for C₁₃H₁₀FN₅O ([M+Na]⁺): 294.0771, found 294.0767.

2-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-4-methylene-1,2,3,4-tetrahydroisoquinoline (**8a**)



Light yellow solid, 290 mg, 74% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 1H), 7.37 – 7.29 (m, 3H), 7.25 – 7.14 (m, 6H), 7.03 (d, *J* = 1.3 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.70 (s, 1H), 5.58 (d, *J* = 15.0 Hz, 1H), 5.36 (s, 1H), 5.23 (d, *J* = 15.0 Hz, 1H), 5.09 (s, 1H), 3.70 (dd, *J* = 27.4, 13.5 Hz, 2H), 3.51 (d, *J* = 13.5 Hz, 1H), 3.28 – 3.20 (m, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.9, 137.7, 136.7, 135.0, 132.7, 130.9, 129.5, 129.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 124.2, 111.0, 57.5, 56.5, 51.4, 50.7. HRMS (ESI) calcd for C₂₅H₂₃N₅ ([M+Na]⁺): 416.1851, found 416.1834.

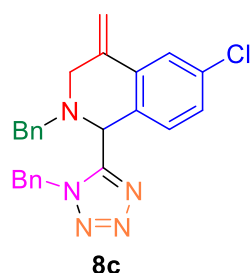
2-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-6-methyl-4-methylene-1,2,3,4-tetrahydroisoquinoline (**8b**)



Colorless oil, 288 mg, 71% yield. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.71 – 7.63 (m, 1H), 7.31 (d, *J* = 2.2 Hz, 2H), 7.30 – 7.28 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 2H), 7.14 (dd, *J* = 7.0, 2.5 Hz, 2H), 7.07 – 6.95 (m, 3H), 6.63 (d, *J* = 7.9 Hz, 1H), 5.82 (s, 1H), 5.78 – 5.70 (m, 1H), 5.51 (t, *J* = 7.7 Hz, 2H), 4.99 (s, 1H), 3.74 – 3.49 (m, 3H), 3.17 (d, *J* = 14.5 Hz, 1H), 2.31 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 156.0, 137.7, 137.6, 136.9, 135.0, 132.4, 129.8, 129.5, 129.1, 129.0, 128.8, 128.6, 128.5, 128.2, 128.1, 127.9, 124.4, 110.7, 57.6, 56.4, 51.6, 50.7, 21.3. HRMS (ESI) calcd for C₂₆H₂₅N₅ ([M+Na]⁺):

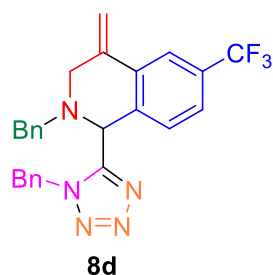
430.2008, found 430.2052.

2-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-6-chloro-4-methylene-1,2,3,4-tetrahydroisoquinoline (**8c**)



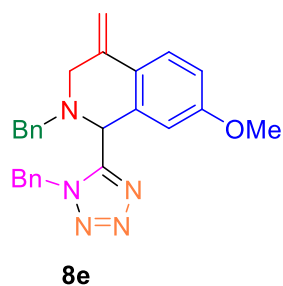
Light yellow solid, 281 mg, 66 % yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 2.2 Hz, 1H), 7.35 – 7.31 (m, 3H), 7.26 (dt, *J* = 5.9, 2.5 Hz, 4H), 7.16 – 7.10 (m, 2H), 7.08 (dd, *J* = 4.5, 1.8 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.97 (s, 1H), 5.74 (d, *J* = 15.5 Hz, 1H), 5.56 (d, *J* = 15.6 Hz, 2H), 5.08 (s, 1H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.57 (d, *J* = 13.1 Hz, 1H), 3.50 (d, *J* = 14.7 Hz, 1H), 3.19 (d, *J* = 14.9 Hz, 1H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 160.4, 142.4, 140.0, 139.8, 139.5, 138.1, 135.7, 134.3, 133.9, 133.6, 133.4, 133.3, 132.8, 132.7, 128.6, 117.8, 62.0, 60.7, 55.4. HRMS (ESI) calcd for C₂₅H₂₂ClN₅ ([M+Na]⁺): 450.1461, found 450.1505.

2-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-4-methylene-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**8d**)



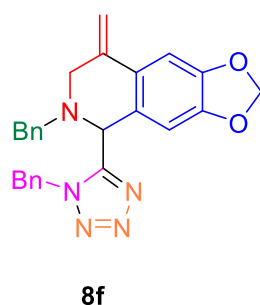
Light yellow solid, 331 mg, 72% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 (d, *J* = 1.9 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.26 (d, *J* = 2.5 Hz, 3H), 7.18 – 7.11 (m, 3H), 7.11 – 7.05 (m, 2H), 6.07 (d, *J* = 1.3 Hz, 1H), 5.77 (d, *J* = 15.5 Hz, 1H), 5.71 (d, *J* = 3.6 Hz, 1H), 5.60 (d, *J* = 15.5 Hz, 1H), 5.15 (s, 1H), 3.71 (d, *J* = 13.1 Hz, 1H), 3.64 – 3.50 (m, 2H), 3.24 (d, *J* = 15.0 Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.5, 137.6, 135.2, 134.0, 134.9, 133.8, 130.3, 129.5, 129.5, 129.3, 129.1, 129.1, 129.1, 129.0, 128.8, 128.6, 128.6, 128.1, 128.0, 127.9, 125.9, 125.0, 124.9, 123.2, 121.1, 121.1, 113.6, 57.3, 56.2, 50.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -61.1. HRMS (ESI) calcd for C₂₆H₂₂F₃N₅ ([M+Na]⁺): 484.1725, found 484.1752.

2-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-7-methoxy-4-methylene-1,2,3,4-tetrahydroisoquinoline (**8e**)



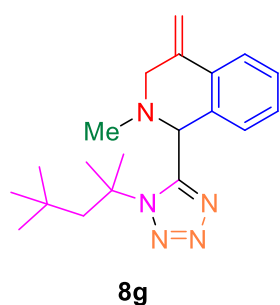
Light yellow solid, 287 mg, 68% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.27 (d, *J* = 1.9 Hz, 2H), 7.19 – 7.10 (m, 2H), 7.10 – 7.01 (m, 2H), 6.91 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.28 (d, *J* = 2.6 Hz, 1H), 5.74 (s, 3H), 5.68 (s, 1H), 5.55 – 5.48 (m, 2H), 4.87 (s, 1H), 3.66 (d, *J* = 13.1 Hz, 1H), 3.61 (s, 3H), 3.17 (d, *J* = 14.7 Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.7, 155.8, 137.8, 136.3, 135.1, 132.2, 129.5, 129.1, 128.8, 128.6, 128.1, 127.9, 125.8, 125.5, 115.1, 112.7, 108.6, 57.5, 56.5, 55.6, 55.3, 51.5, 50.7. HRMS (ESI) calcd for C₂₆H₂₅N₅O ([M+Na]⁺): 446.1957, found 446.1961.

6-benzyl-5-(1-benzyl-1H-tetrazol-5-yl)-8-methylene-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (**8f**)



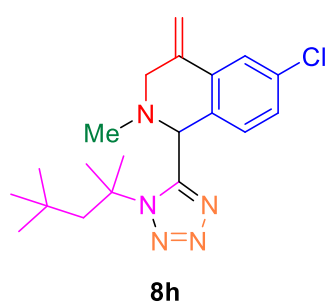
Light yellow solid, 319 mg, 73% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.39 (s, 1H), 7.36 – 7.30 (m, 3H), 7.27 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.17 – 7.10 (m, 2H), 7.09 – 7.02 (m, 2H), 6.27 (s, 1H), 6.02 (d, *J* = 1.0 Hz, 1H), 5.98 (d, *J* = 1.0 Hz, 1H), 5.74 – 5.68 (m, 2H), 5.52 (d, *J* = 15.4 Hz, 1H), 5.42 (s, 1H), 4.89 (s, 1H), 3.74 – 3.55 (m, 2H), 3.54 – 3.45 (m, 1H), 3.14 (d, *J* = 14.7 Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.9, 148.1, 148.0, 137.8, 136.4, 135.1, 129.5, 129.1, 128.8, 128.6, 128.1, 127.9, 127.0, 124.7, 109.7, 107.8, 103.7, 101.7, 57.4, 56.5, 51.3, 50.6. HRMS (ESI) calcd for C₂₆H₂₃N₅O₂ ([M+Na]⁺): 460.1749, found 460.1803.

2-methyl-4-methylene-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (8g)



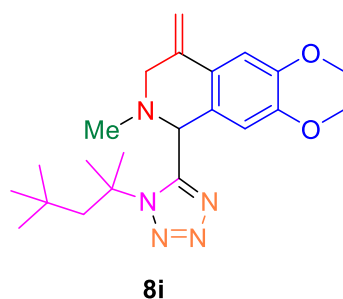
White solid, 230 mg, 68% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H), 5.76 (s, 1H), 5.33 (s, 1H), 5.12 (s, 1H), 3.85 (d, J = 14.4 Hz, 1H), 3.23 (d, J = 14.4 Hz, 1H), 2.43 (s, 3H), 2.11 (d, J = 14.7 Hz, 2H), 1.81 (s, 6H), 0.85 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.0, 132.4, 128.4, 127.8, 123.8, 110.0, 53.3, 31.6, 30.8, 29.8. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{29}\text{N}_5$ ($[\text{M}+\text{Na}]^+$): 362.2321, found 362.2314.

6-chloro-2-methyl-4-methylene-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (8h)



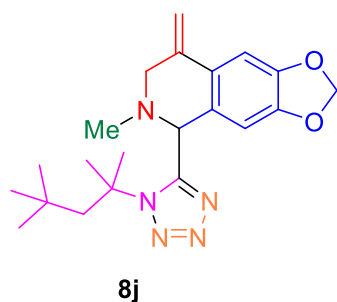
Light yellow solid, 257 mg, 69% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, J = 2.2 Hz, 1H), 7.16 (dd, J = 8.2, 2.1 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.72 (s, 1H), 5.23 (s, 1H), 5.13 (s, 1H), 3.77 (d, J = 14.8 Hz, 1H), 3.18 (d, J = 14.7 Hz, 1H), 2.40 (s, 3H), 2.19 (d, J = 15.3 Hz, 1H), 2.05 (d, J = 14.9 Hz, 1H), 1.80 (s, 6H), 0.82 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.5, 134.2, 133.9, 129.6, 128.5, 123.8, 111.6, 66.3, 53.3, 31.6, 30.8, 30.1, 29.7. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{28}\text{ClN}_5$ ($[\text{M}+\text{Na}]^+$): 396.1931, found 396.1923.

6,7-dimethoxy-2-methyl-4-methylene-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (8i)



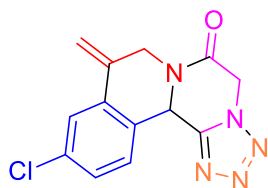
Light yellow solid, 263 mg, 66% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.16 (s, 1H), 6.18 (s, 1H), 5.54 (s, 1H), 5.22 (s, 1H), 4.99 (s, 1H), 3.90 (s, 3H), 3.74 (dd, J = 14.3, 2.7 Hz, 1H), 3.69 (s, 3H), 3.16 (d, J = 14.3 Hz, 1H), 2.38 (s, 3H), 2.13 (d, J = 10.3 Hz, 2H), 1.76 (d, J = 8.8 Hz, 6H), 0.82 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.07, 149.6, 148.7, 125.2, 108.0, 105.9, 55.9, 55.8, 53.3, 31.6, 30.9, 30.1. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{33}\text{N}_5\text{O}_2$ ($[\text{M}+\text{Na}]^+$): 422.2532, found 422.2106

6-methyl-8-methylene-5-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (8j)



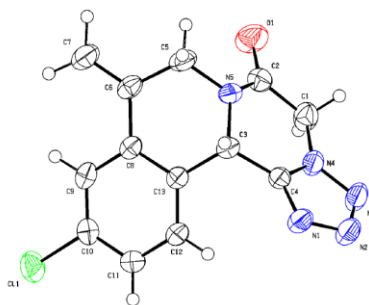
White solid, 252 mg, 66% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.18 (s, 1H), 6.22 (s, 1H), 5.94 (d, J = 1.2 Hz, 1H), 5.91 (d, J = 1.3 Hz, 1H), 5.53 (s, 1H), 5.15 (s, 1H), 4.98 (s, 1H), 3.75 (d, J = 14.6 Hz, 1H), 3.13 (d, J = 14.6 Hz, 1H), 2.41 (s, 3H), 2.20 (d, J = 15.4 Hz, 1H), 2.06 (s, 1H), 1.83 (d, J = 13.0 Hz, 6H), 0.84 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.9, 148.1, 147.7, 126.7, 108.6, 107.3, 103.4, 101.2, 53.2, 31.6, 30.8, 29.6. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{29}\text{N}_5\text{O}_2$ ($[\text{M}+\text{Na}]^+$): 406.2219, found 406.2231.

7. X-ray Report of 6d and 8c

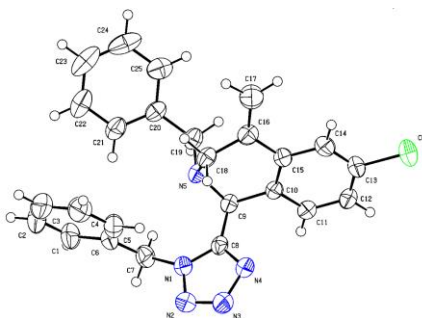
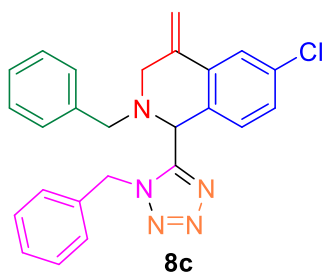


6d

CCDC: 2164364



Bond precision:	C-C = 0.0020 Å	Wavelength=0.71073	
Cell:	a=8.5083 (11)	b=14.3480 (17)	c=10.4672 (13)
	alpha=90	beta=105.064 (2)	gamma=90
Temperature:	296 K		
	Calculated	Reported	
Volume	1233.9 (3)	1233.9 (3)	
Space group	P 21/c	P 21/c	
Hall group	-P 2ybc	-P 2ybc	
Moiety formula	C13 H10 Cl N5 O	?	
Sum formula	C13 H10 Cl N5 O	C13 H10 Cl N5 O	
Mr	287.71	287.71	
Dx, g cm ⁻³	1.549	1.549	
Z	4	4	
Mu (mm ⁻¹)	0.313	0.313	
F000	592.0	592.0	
F000'	592.78		
h, k, lmax	10, 17, 12	10, 17, 12	
Nref	2165	2159	
Tmin, Tmax	0.922, 0.928		
Tmin'	0.922		
Correction method=	Not given		
Data completeness=	0.997	Theta (max)= 24.993	
R(reflections)=	0.0316 (1864)	wR2(reflections)=	
		0.0829 (2159)	
S =	1.086	Npar= 190	



CCDC: 2321622

Bond precision: C-C = 0.0034 Å

Wavelength=0.71073

Cell: a=21.3467 (15)

b=14.9952 (11)

c=6.8948 (5)

alpha=90

beta=90.794 (1)

gamma=90

Temperature: 296 K

	Calculated	Reported
Volume	2206.8 (3)	2206.8 (3)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C ₂₅ H ₂₂ Cl N ₅	?
Sum formula	C ₂₅ H ₂₂ Cl N ₅	C ₂₅ H ₂₂ Cl N ₅
Mr	427.93	427.92
D _x , g cm ⁻³	1.288	1.288
Z	4	4
Mu (mm ⁻¹)	0.195	0.195
F ₀₀₀	896.0	896.0
F ₀₀₀ '	896.86	
h, k, lmax	25, 17, 8	25, 17, 8
N _{ref}	3888	3882
T _{min} , T _{max}	0.954, 0.973	
T _{min} '	0.951	

Correction method= Not given

Data completeness= 0.998

Theta (max)= 24.999

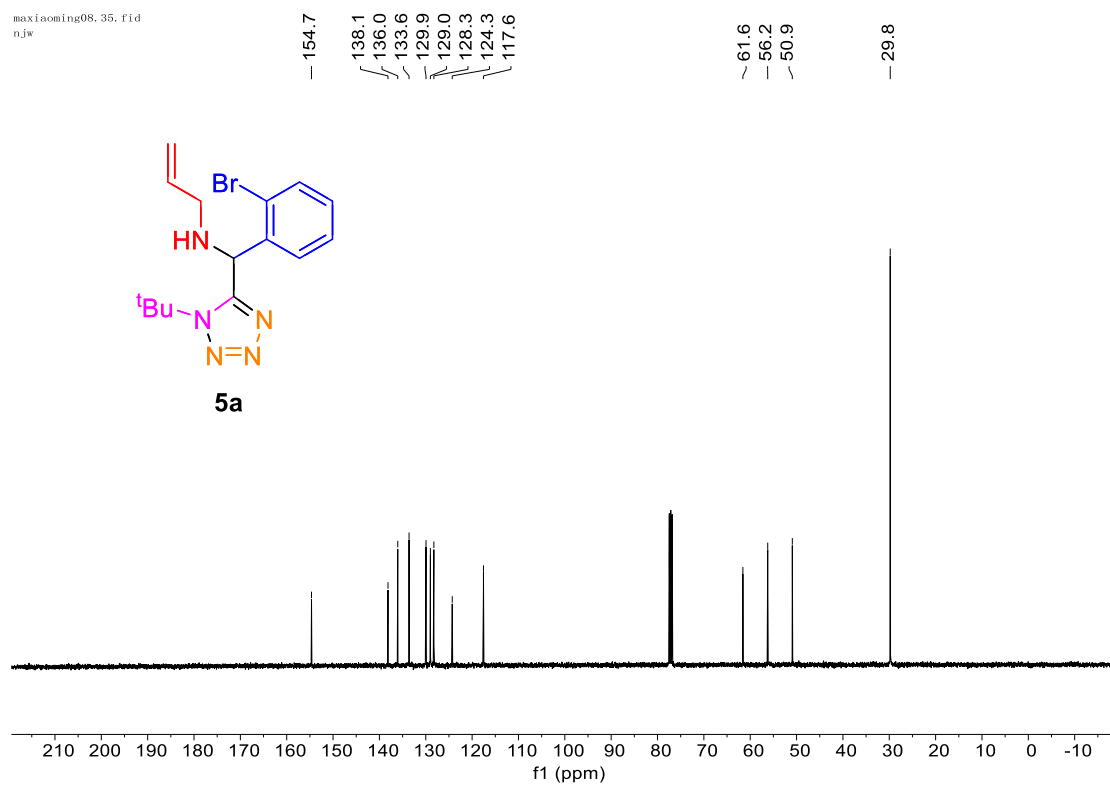
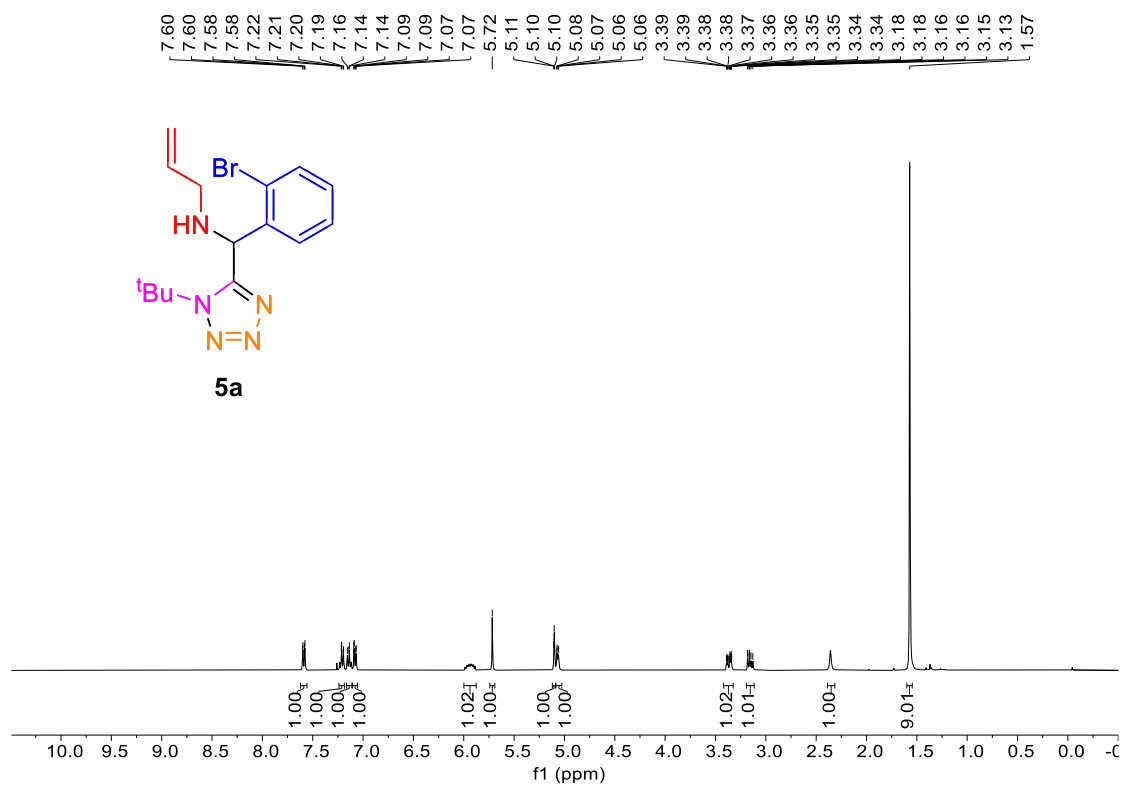
R(reflections)= 0.0424 (2407)

wR2 (reflections)=
0.1147 (3882)

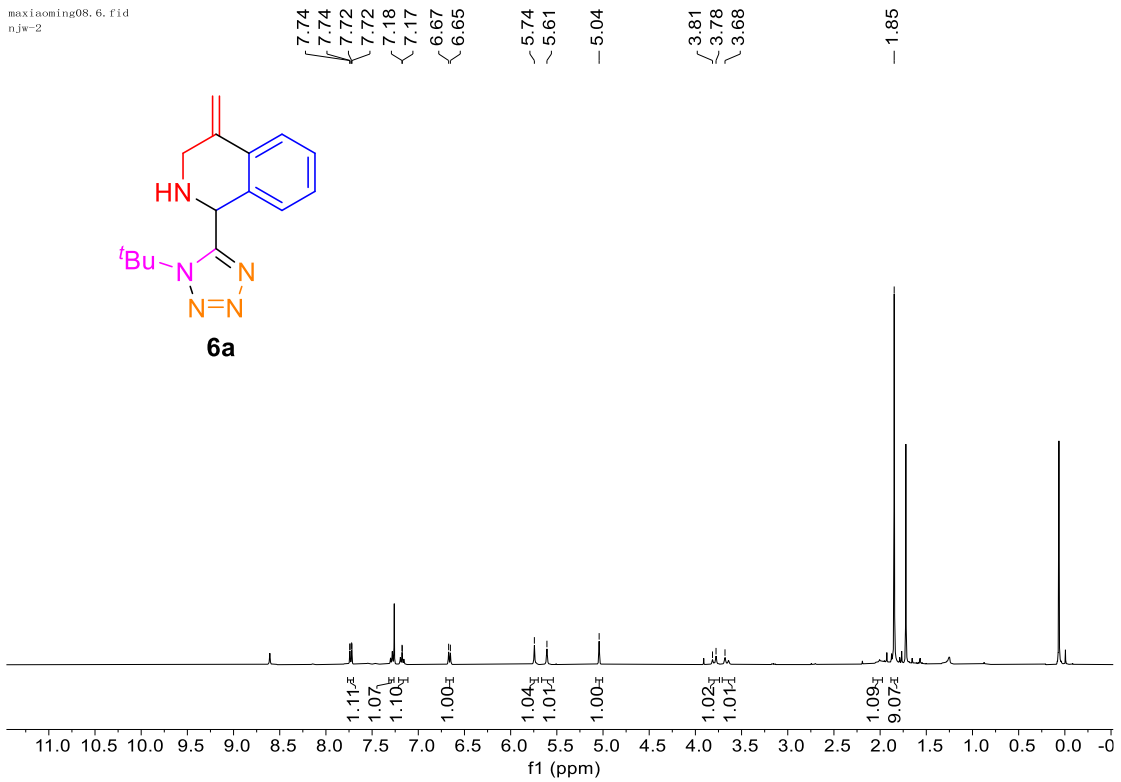
S = 0.862

N_{par}= 288

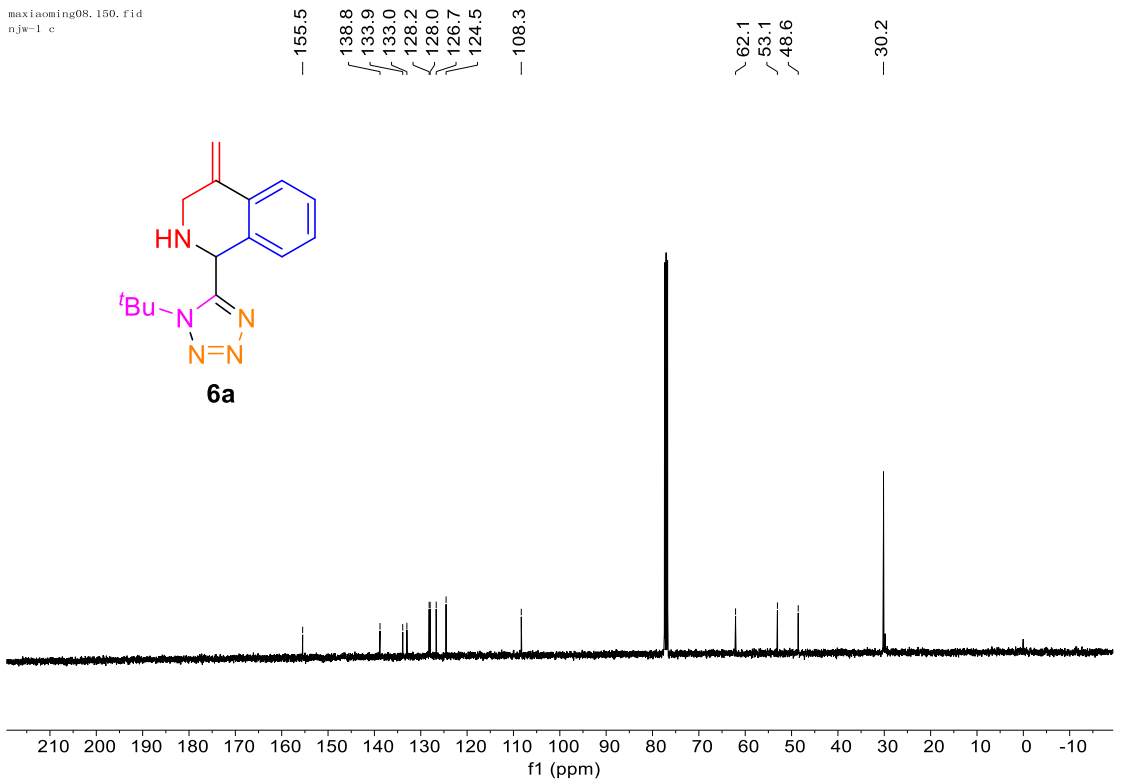
8. $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ of products 5a, 6 and 8



maxiaoming08.6.fid
njw-2

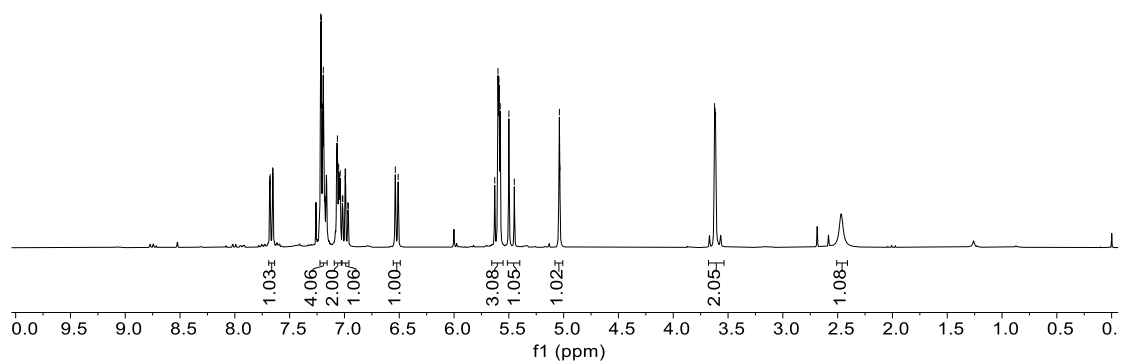
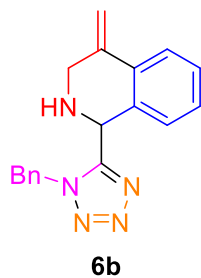


maxiaoming08.150.fid
njw-1 c



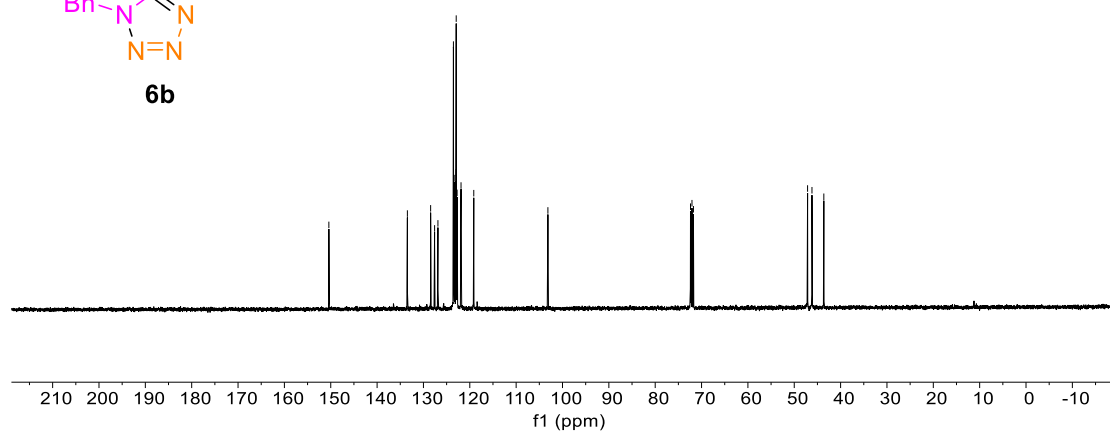
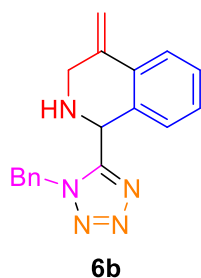
3maxim08.148.fid
nwj-2

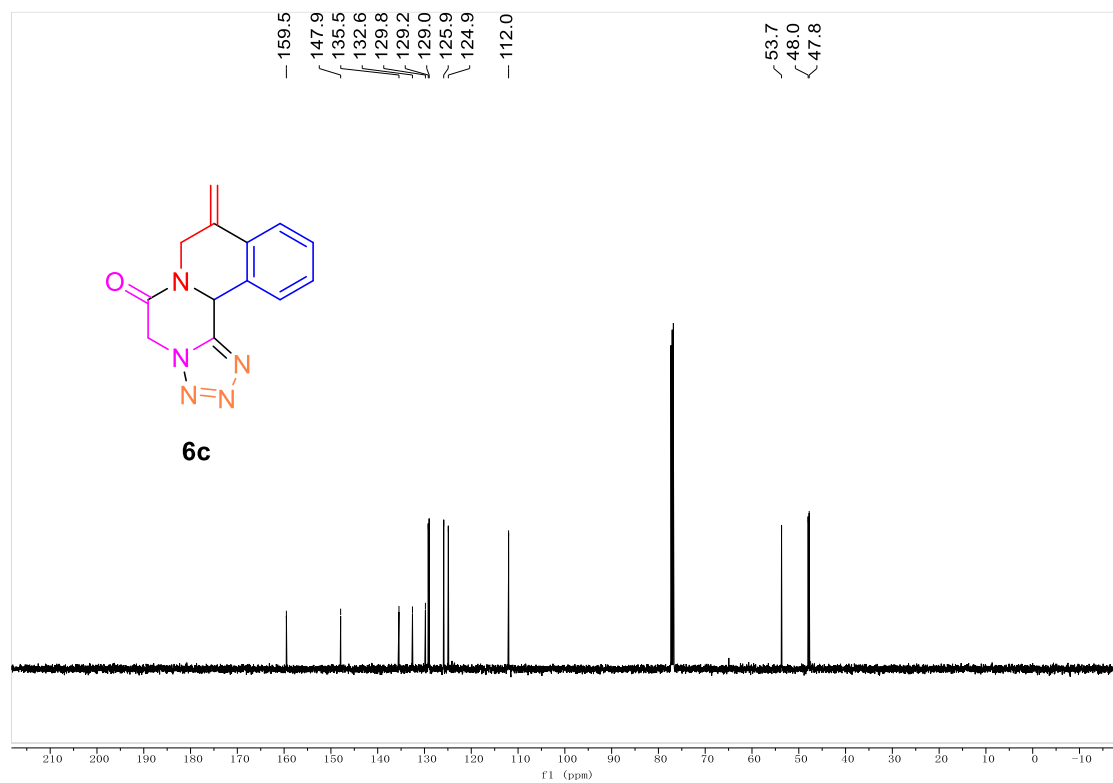
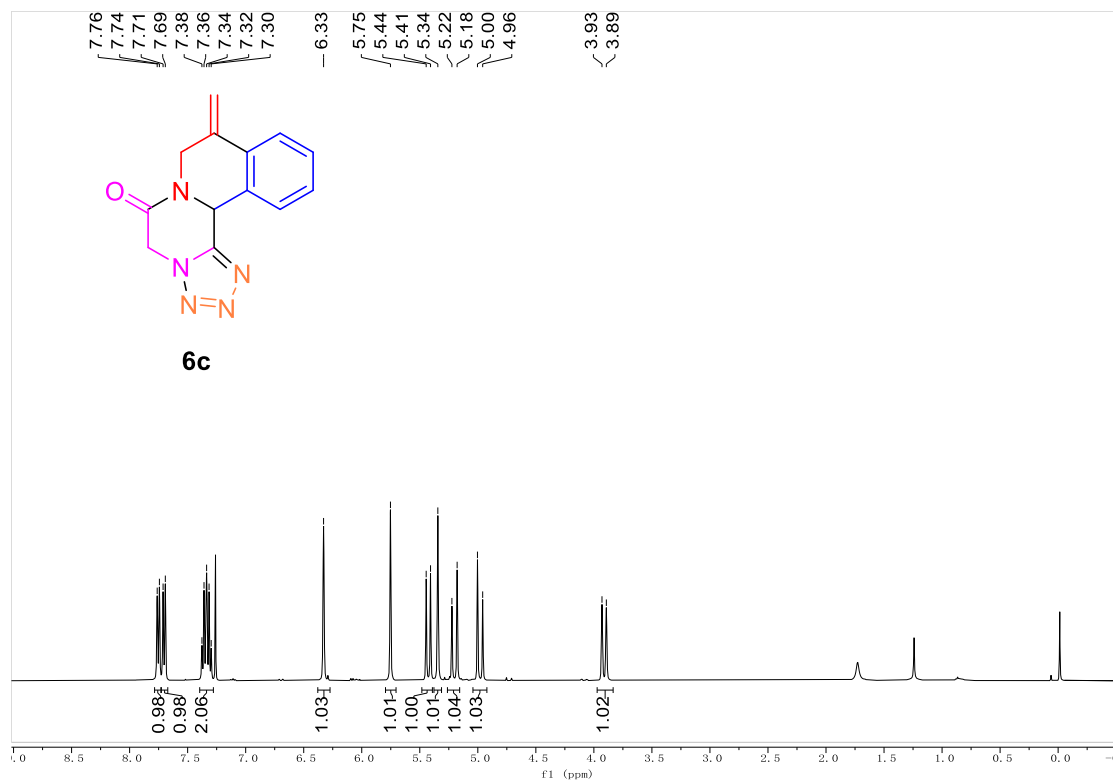
7.68
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7.07
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7.02
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6.99
6.97
6.96
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5.58
5.50
5.45
5.04
5.03
3.62
3.61

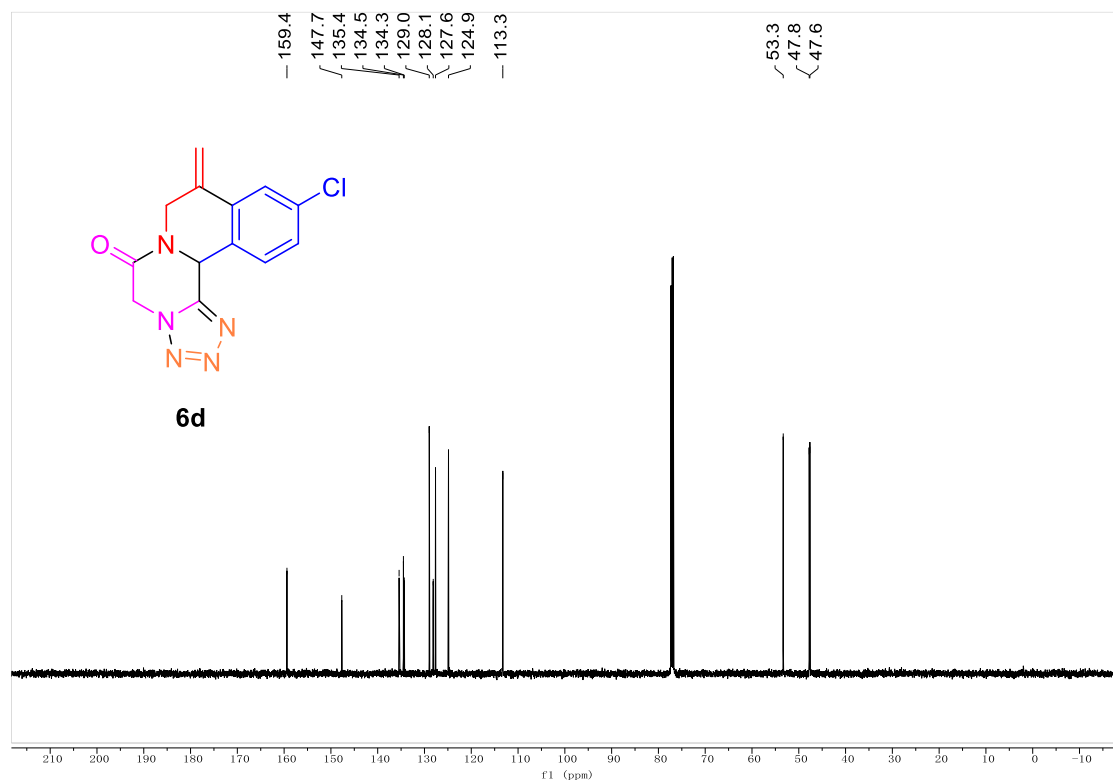
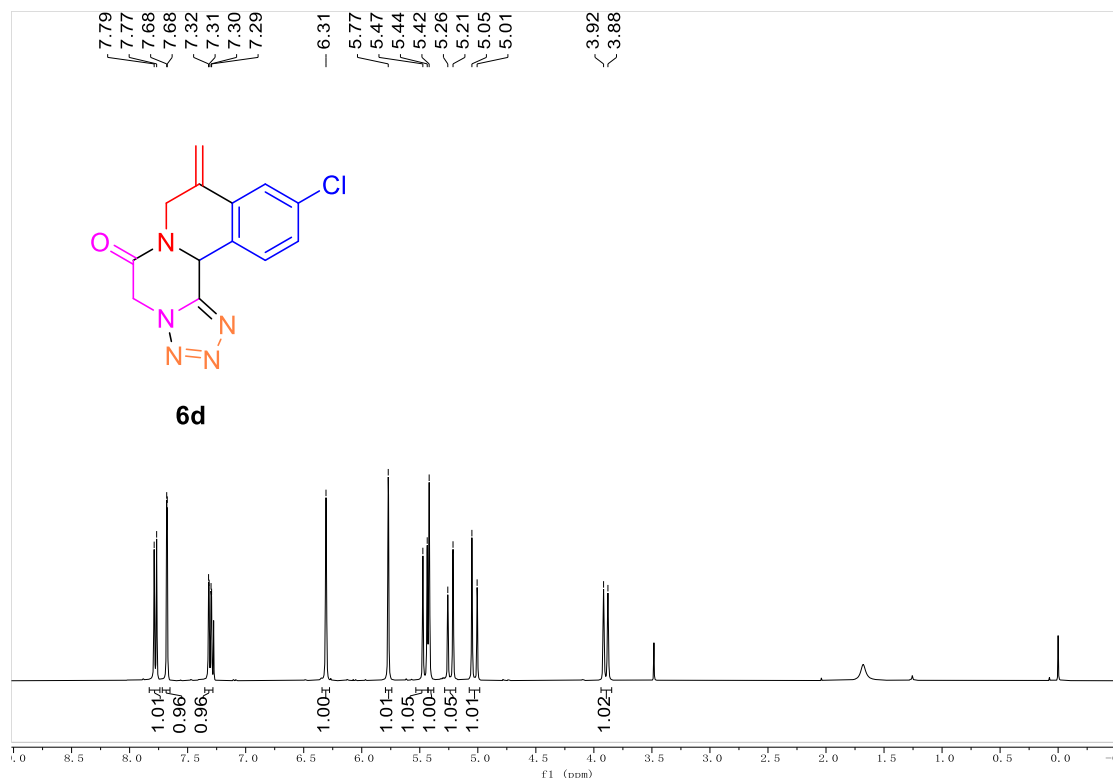


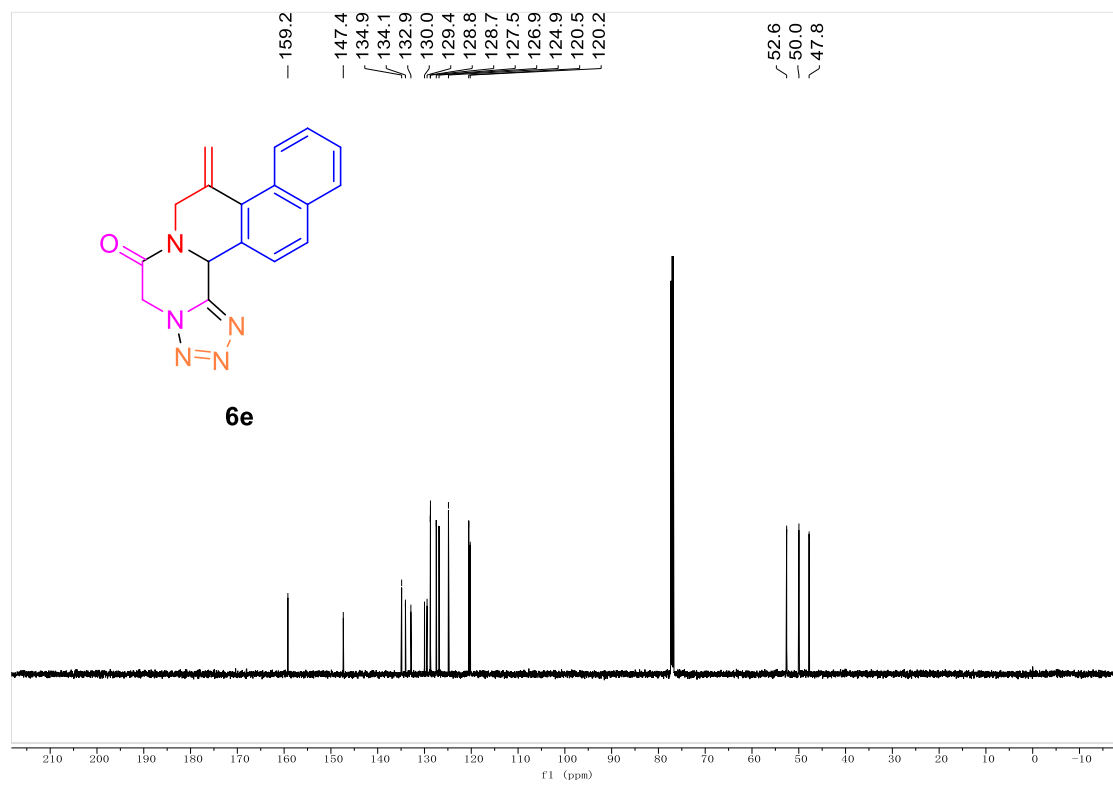
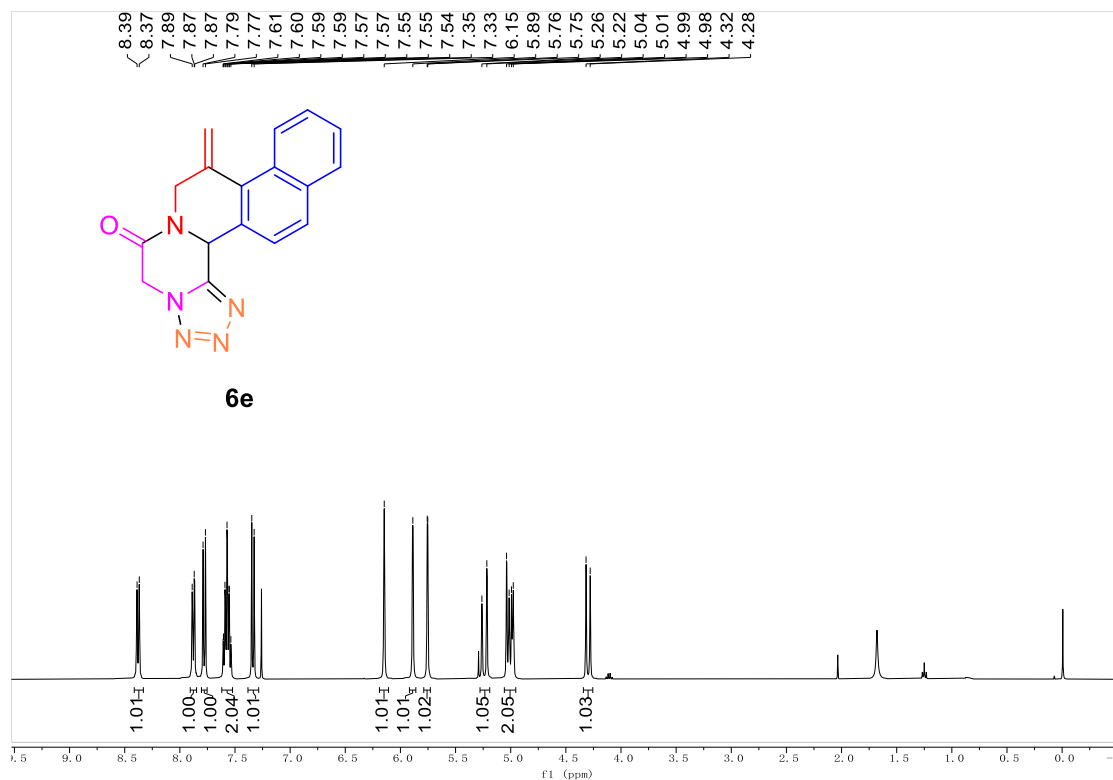
maxiaomg08.148.fid
nwj-2

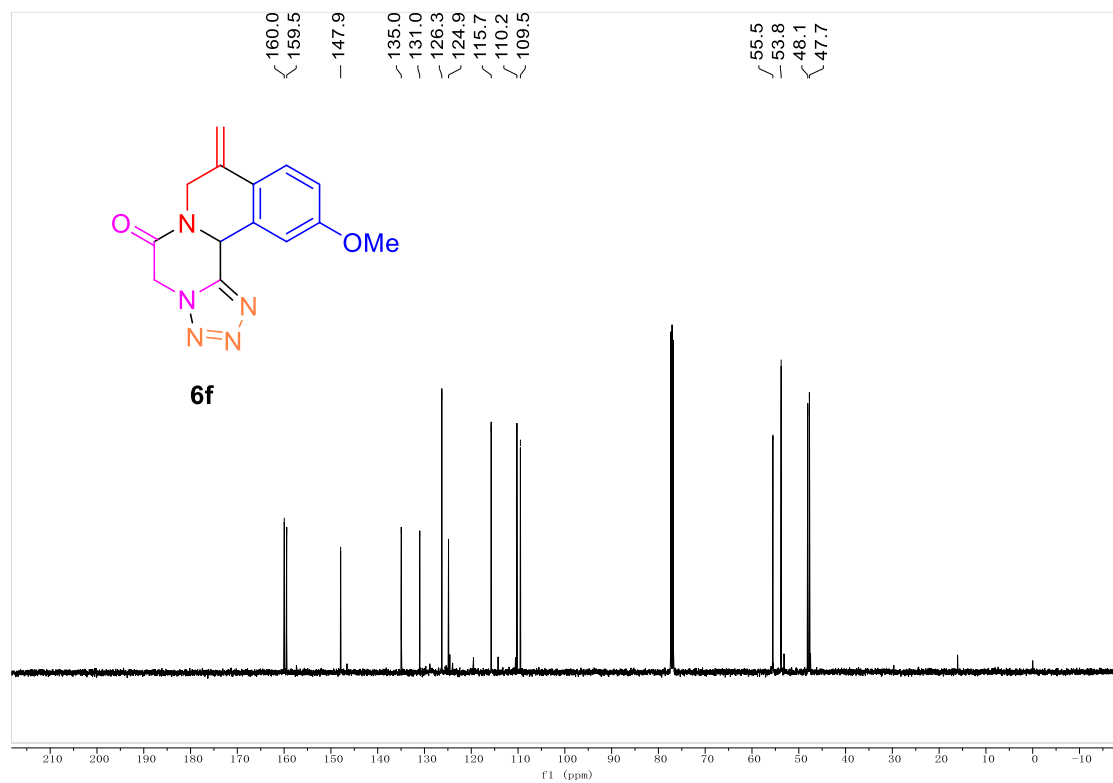
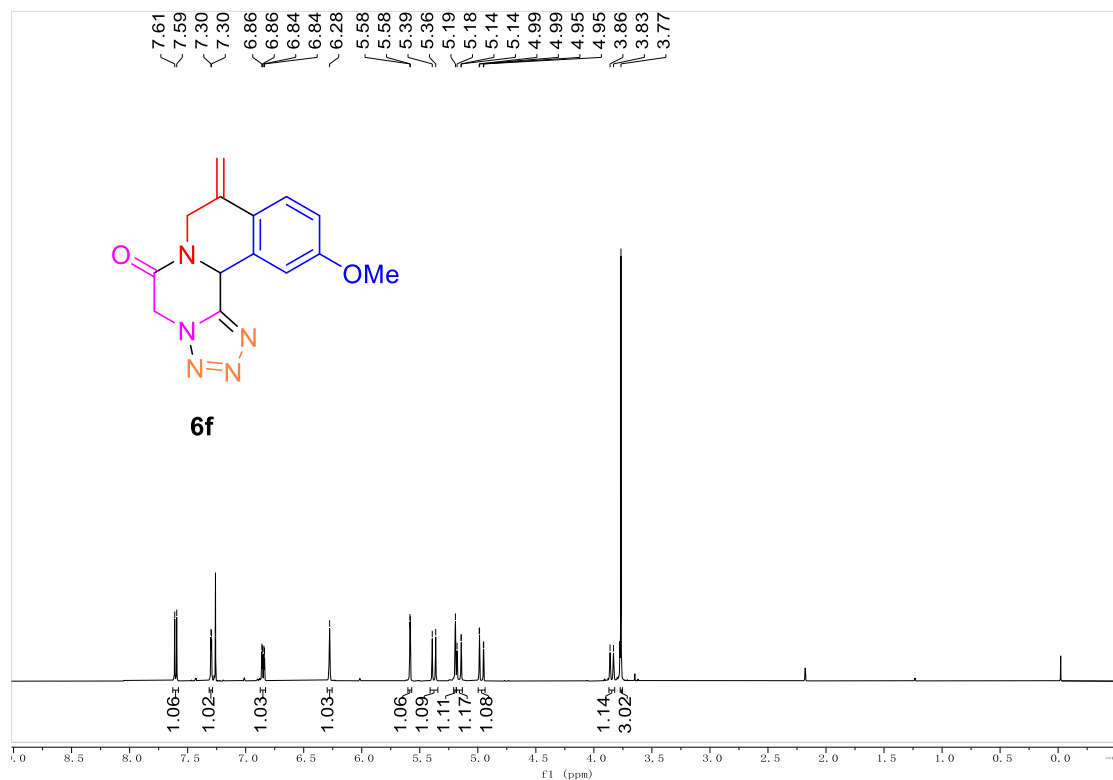
150.4
133.5
128.4
127.6
126.9
123.5
123.2
123.0
122.9
122.7
121.9
119.1
103.2
72.4
72.1
71.7
47.1
46.2
43.6

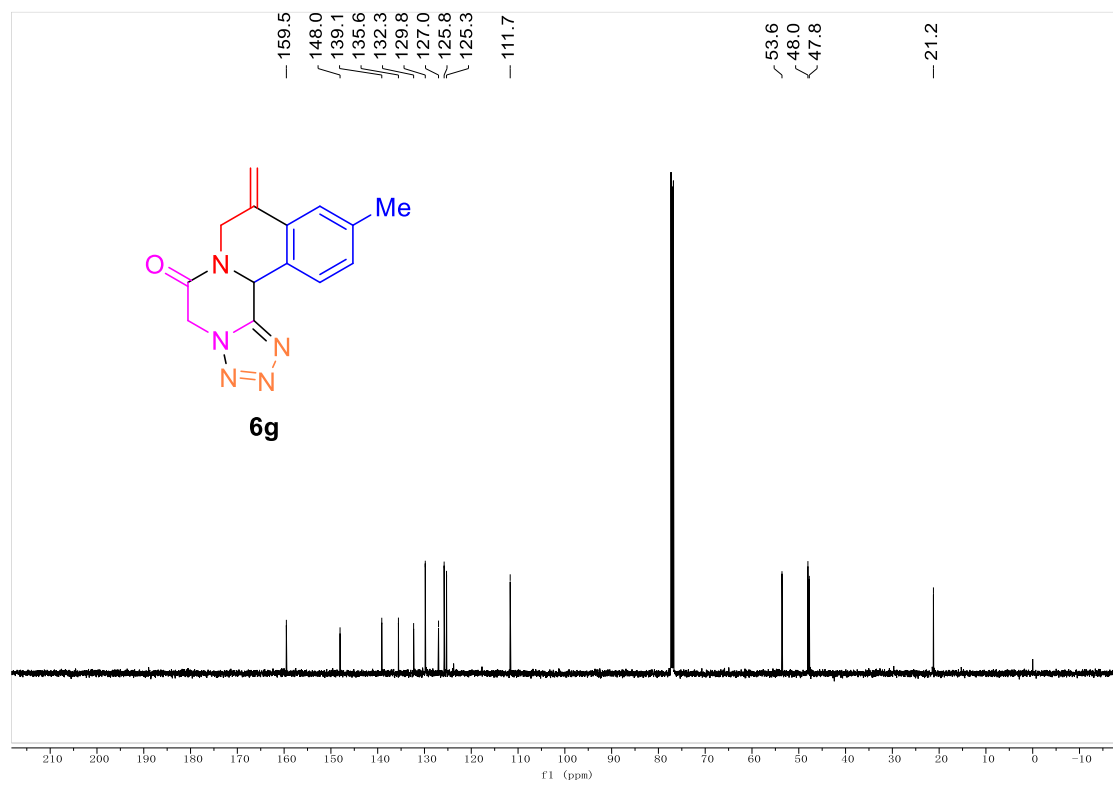
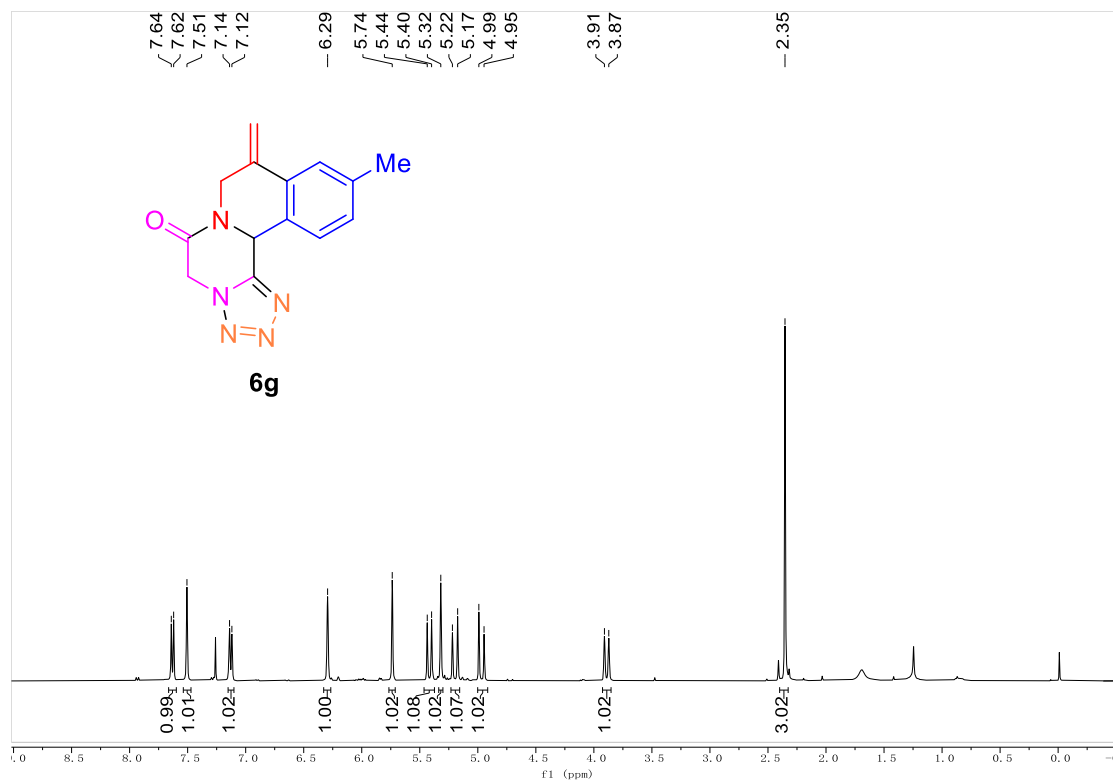


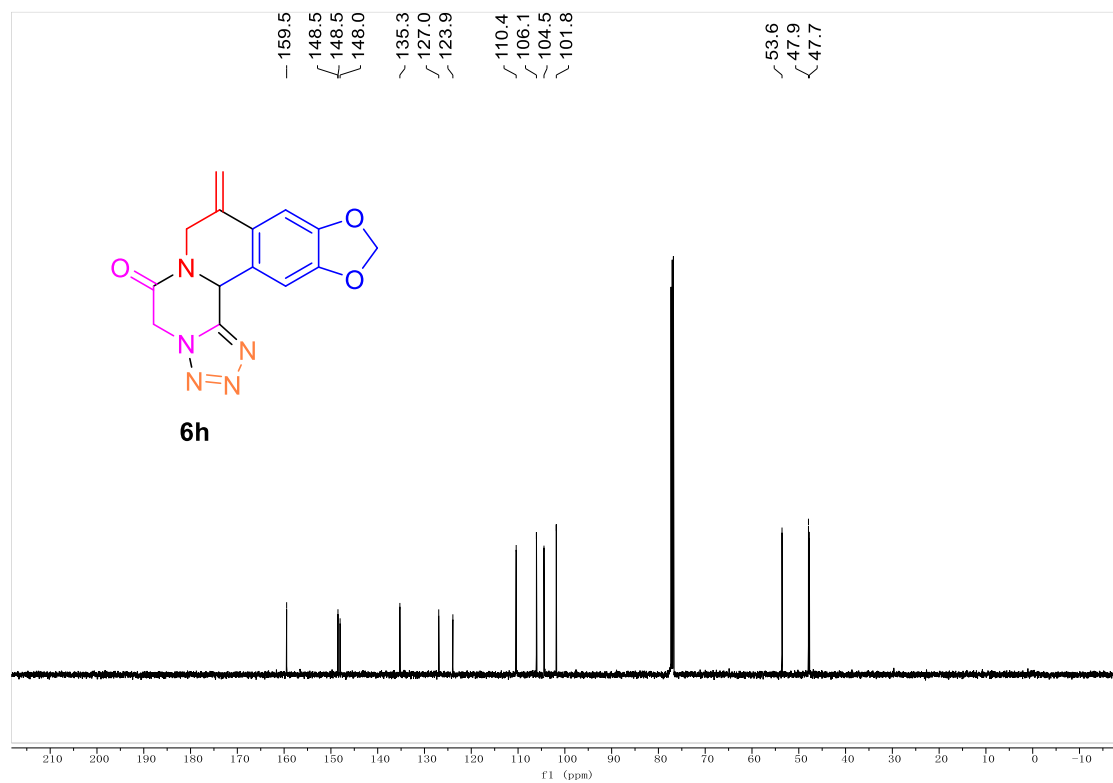
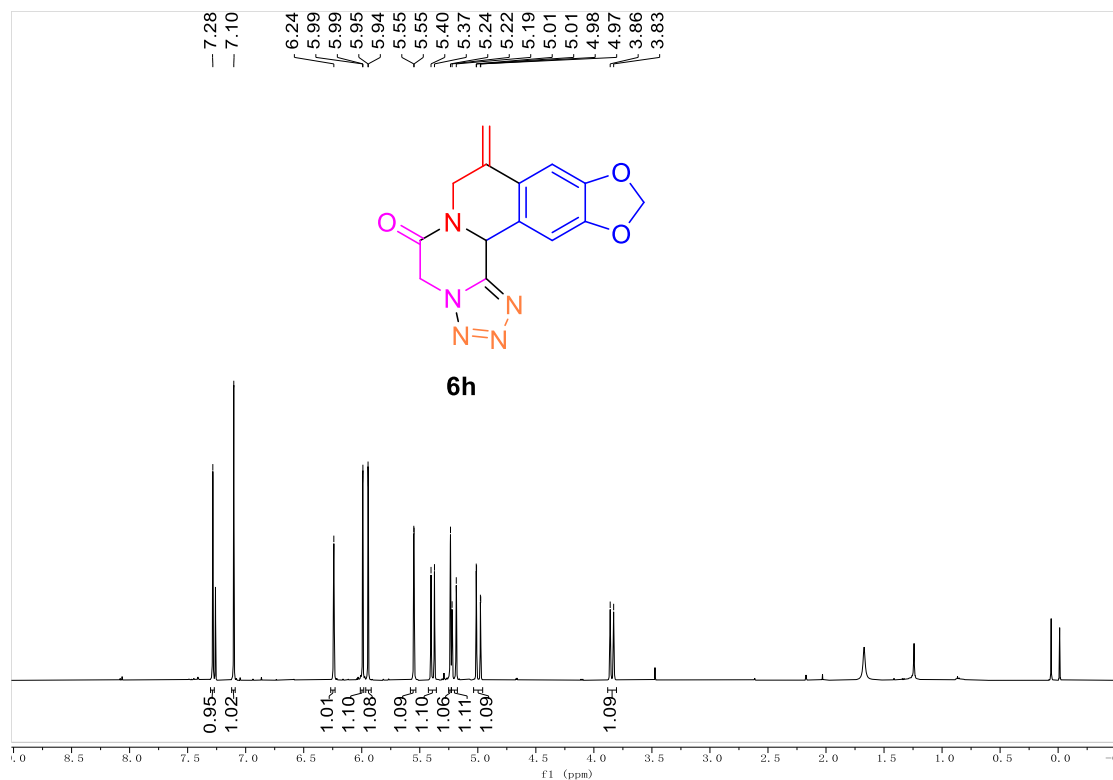


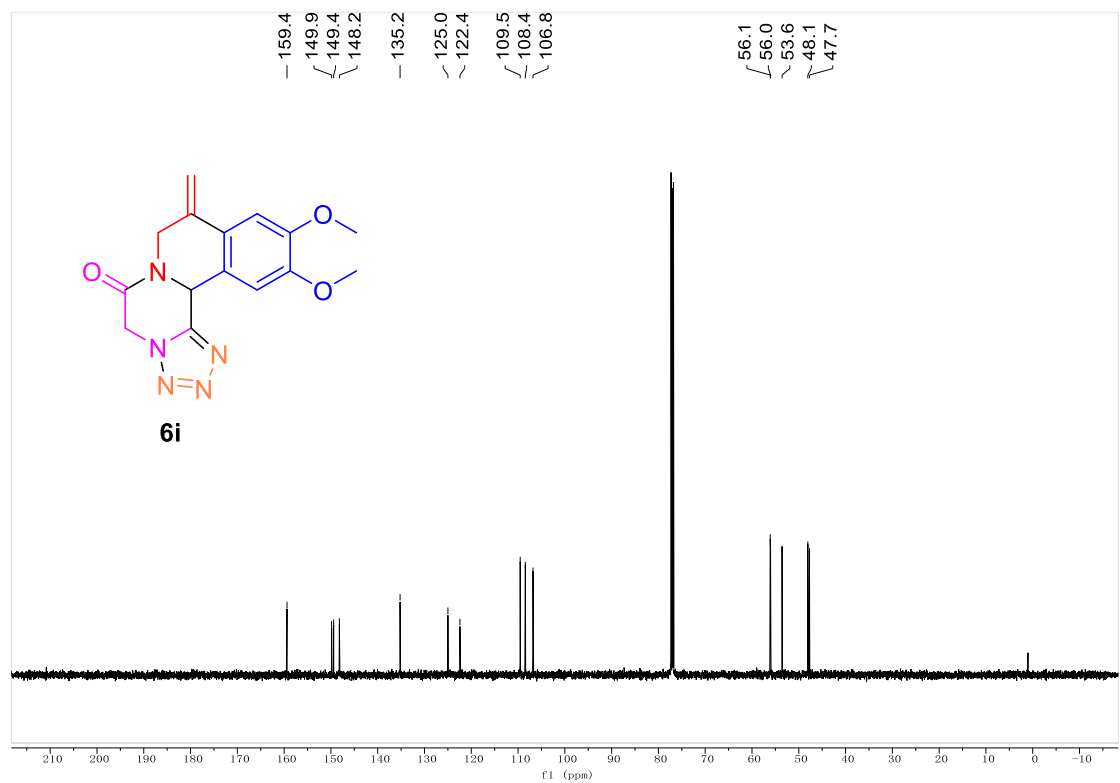
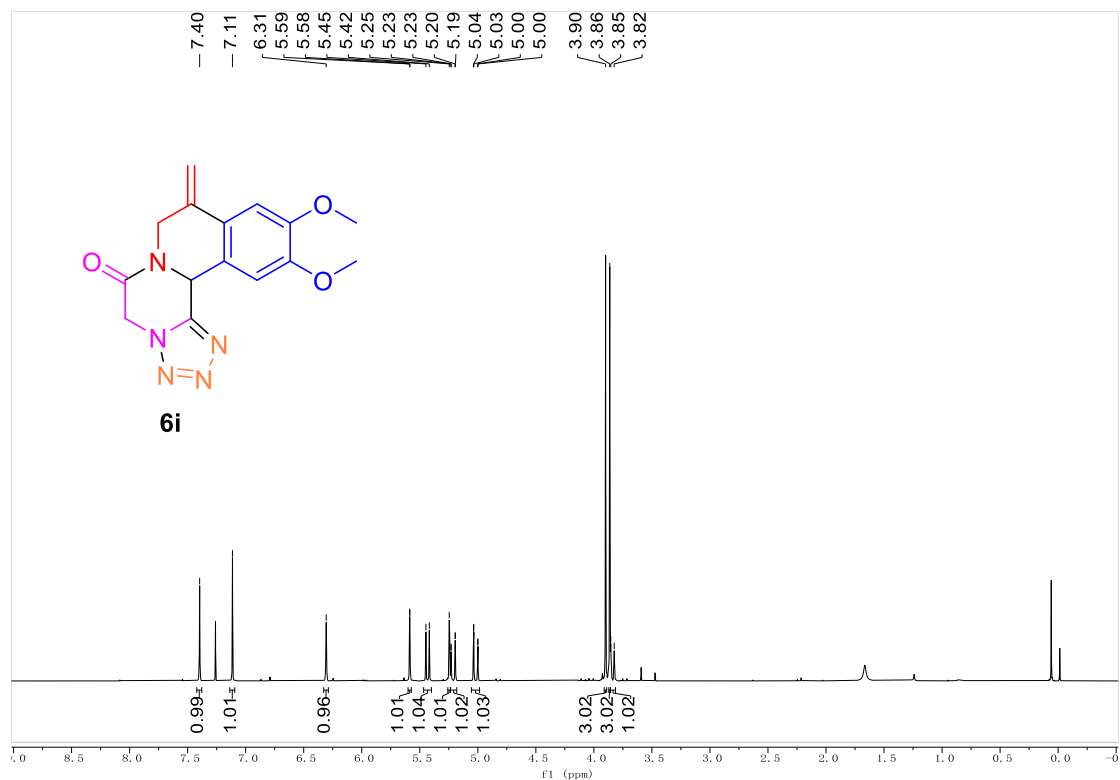


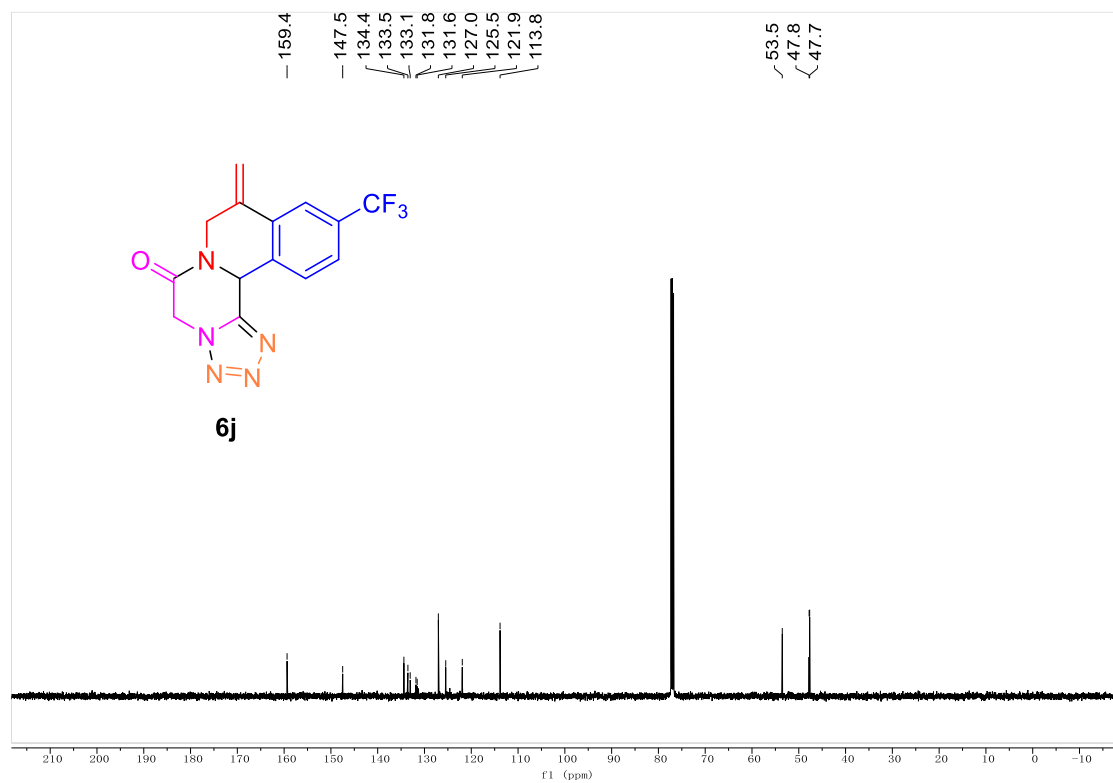
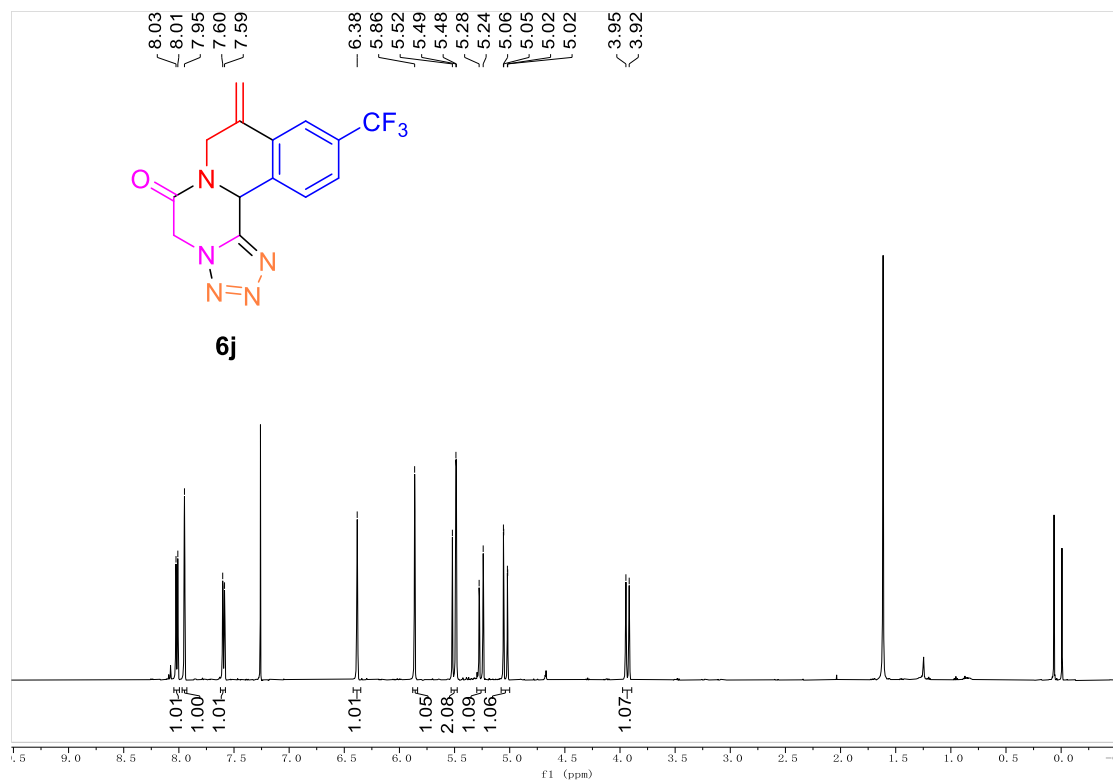


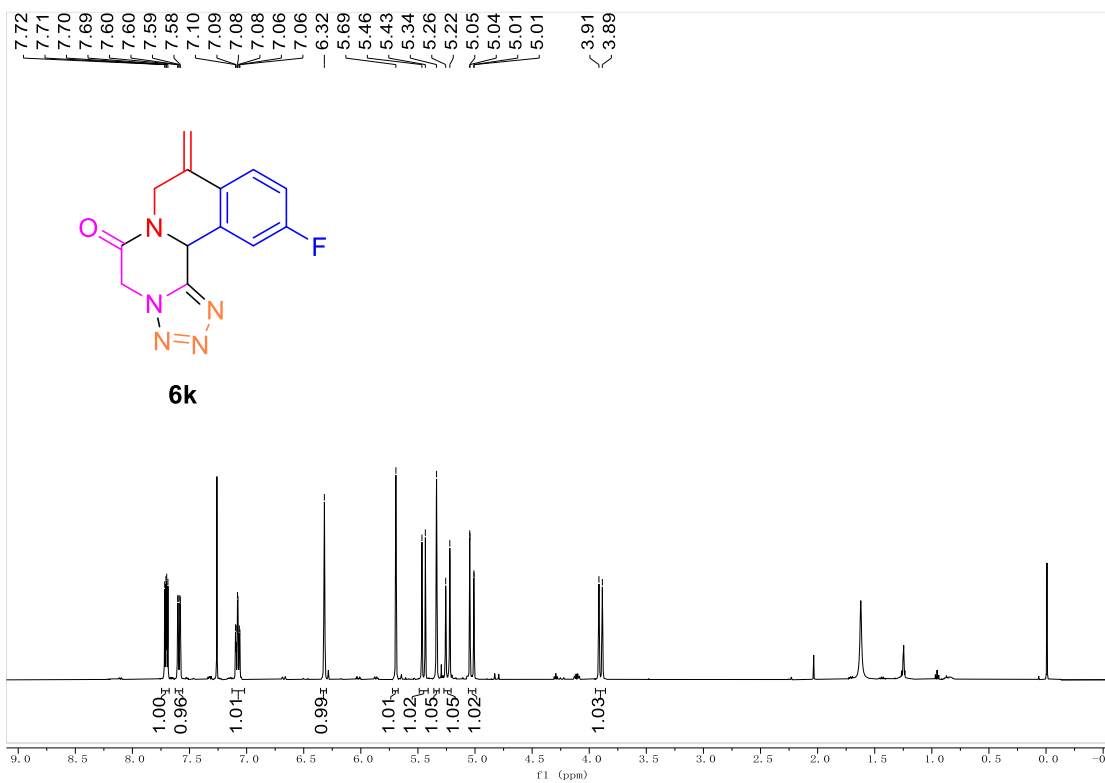
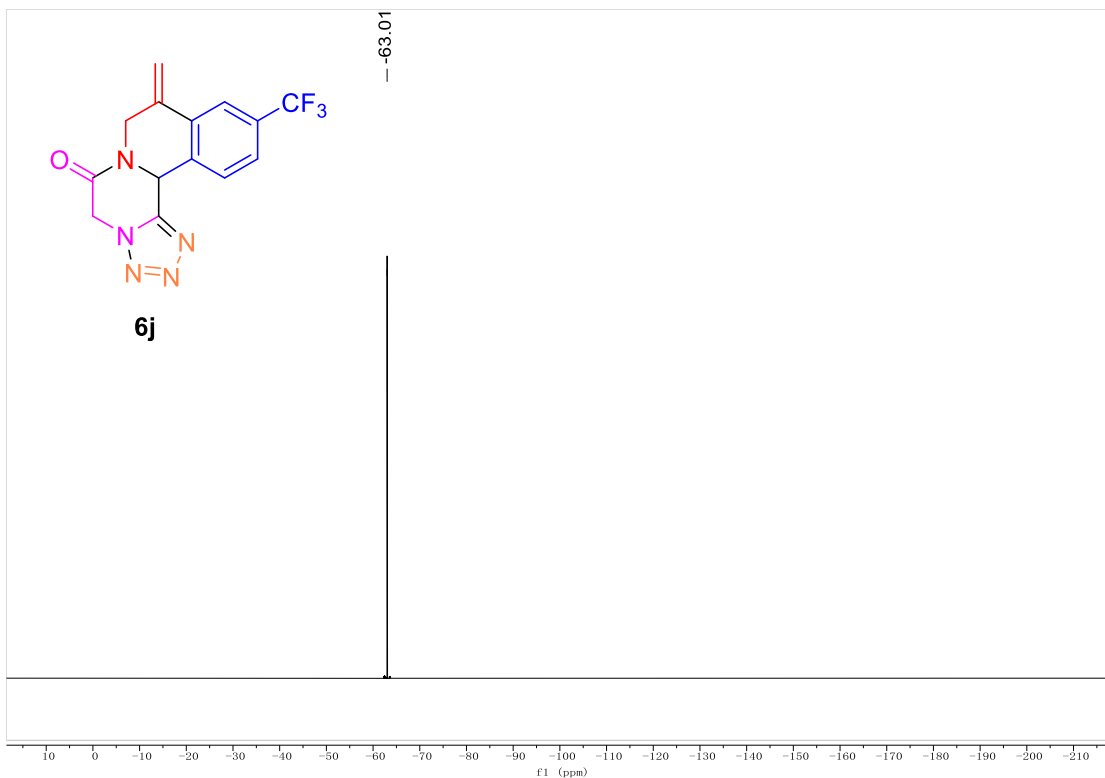


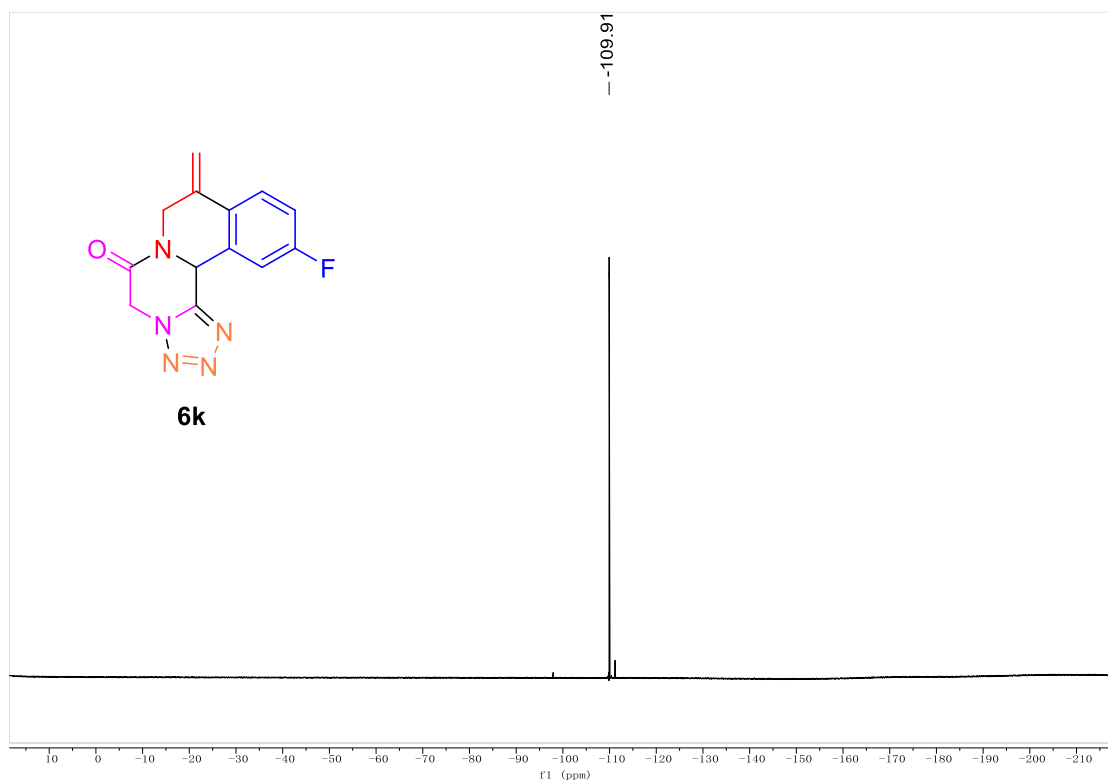
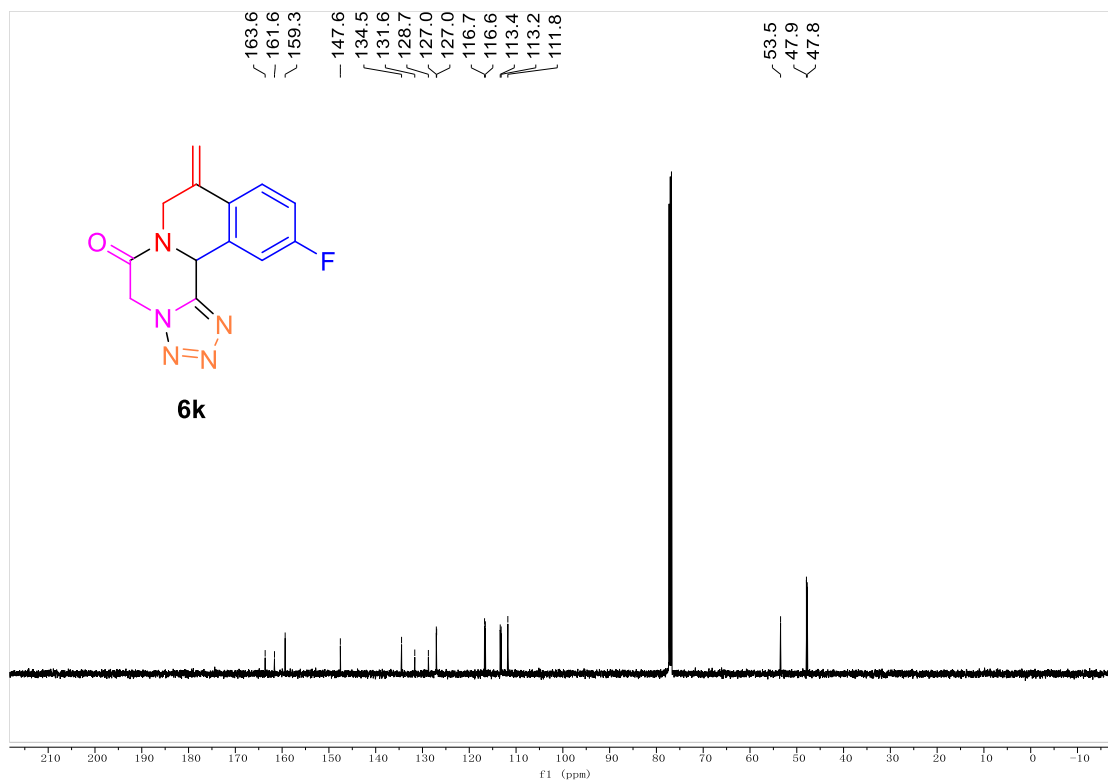


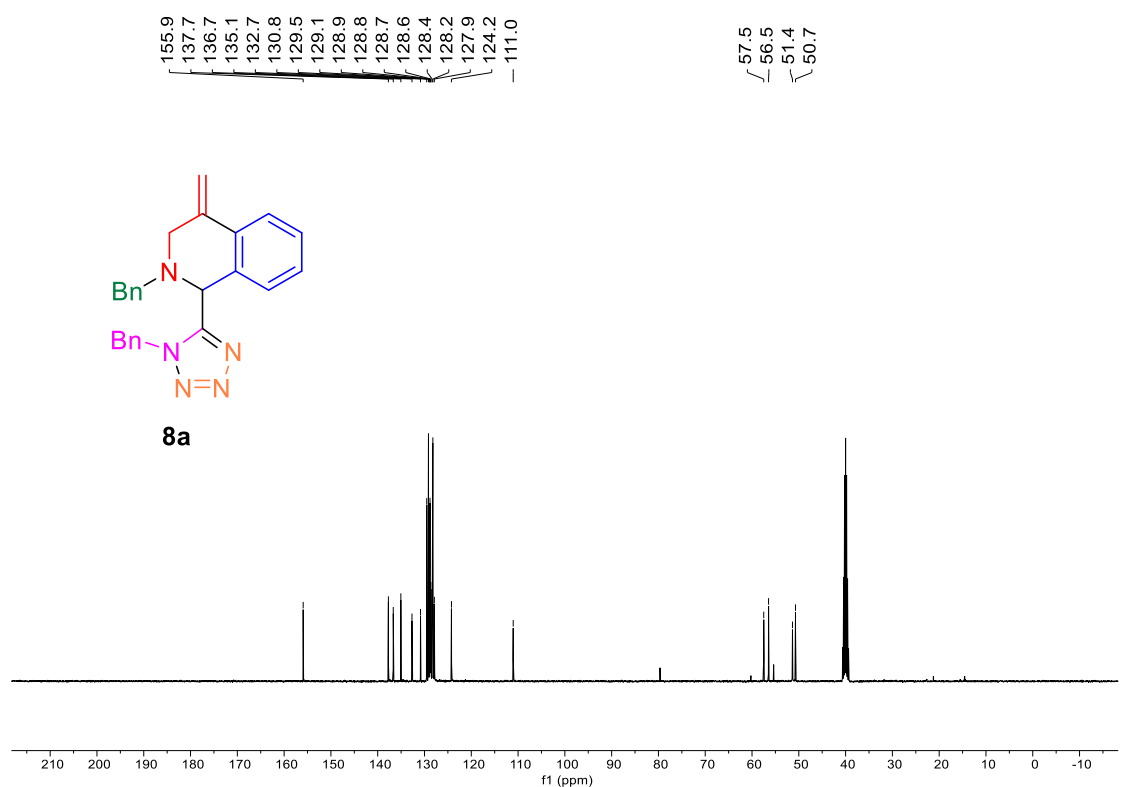
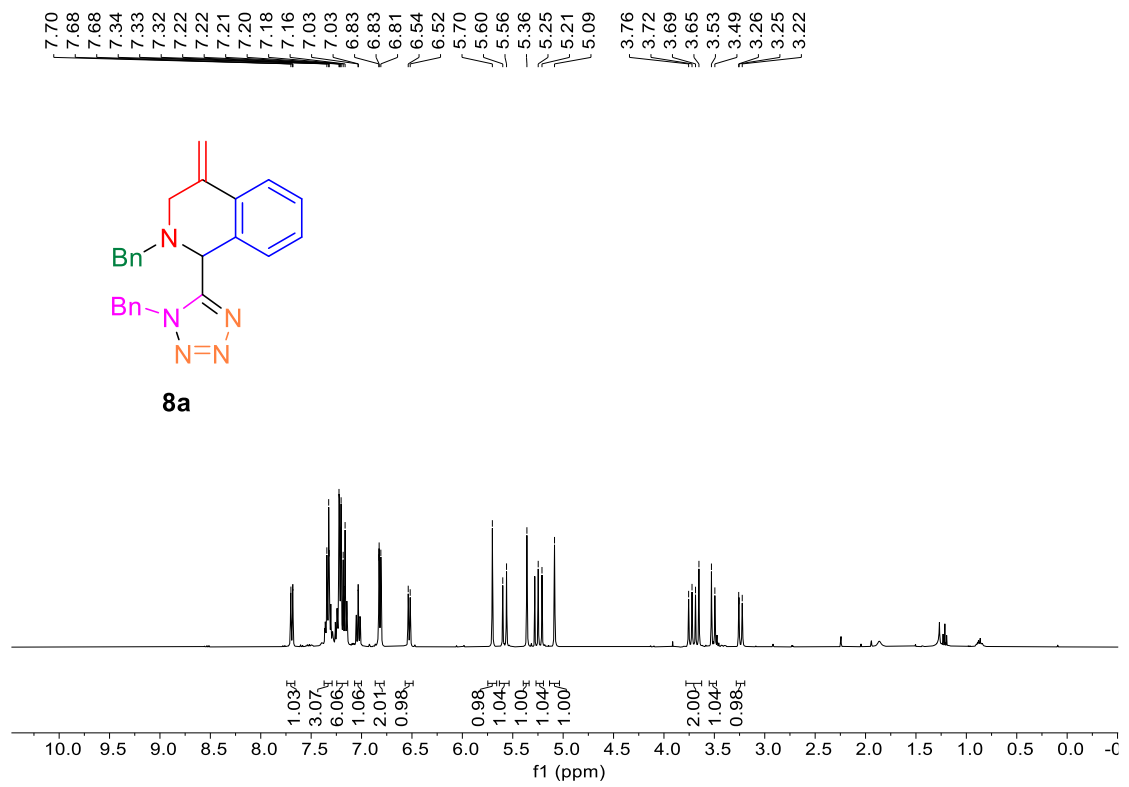


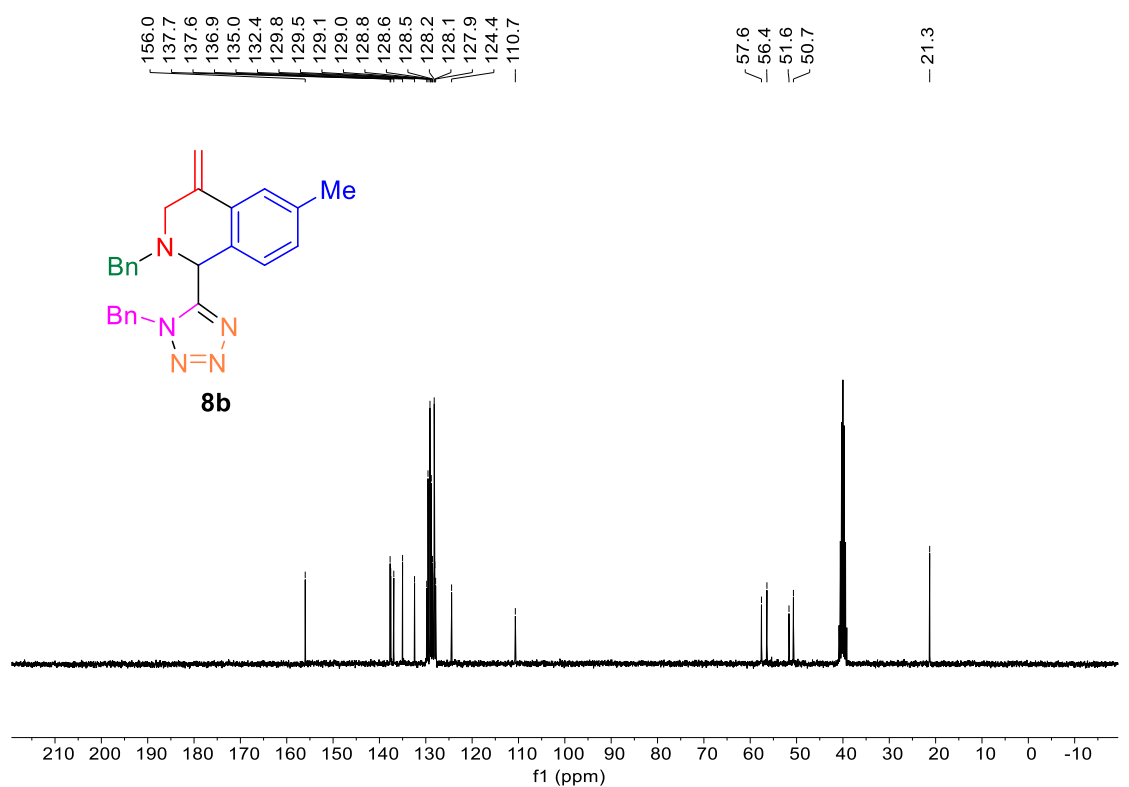
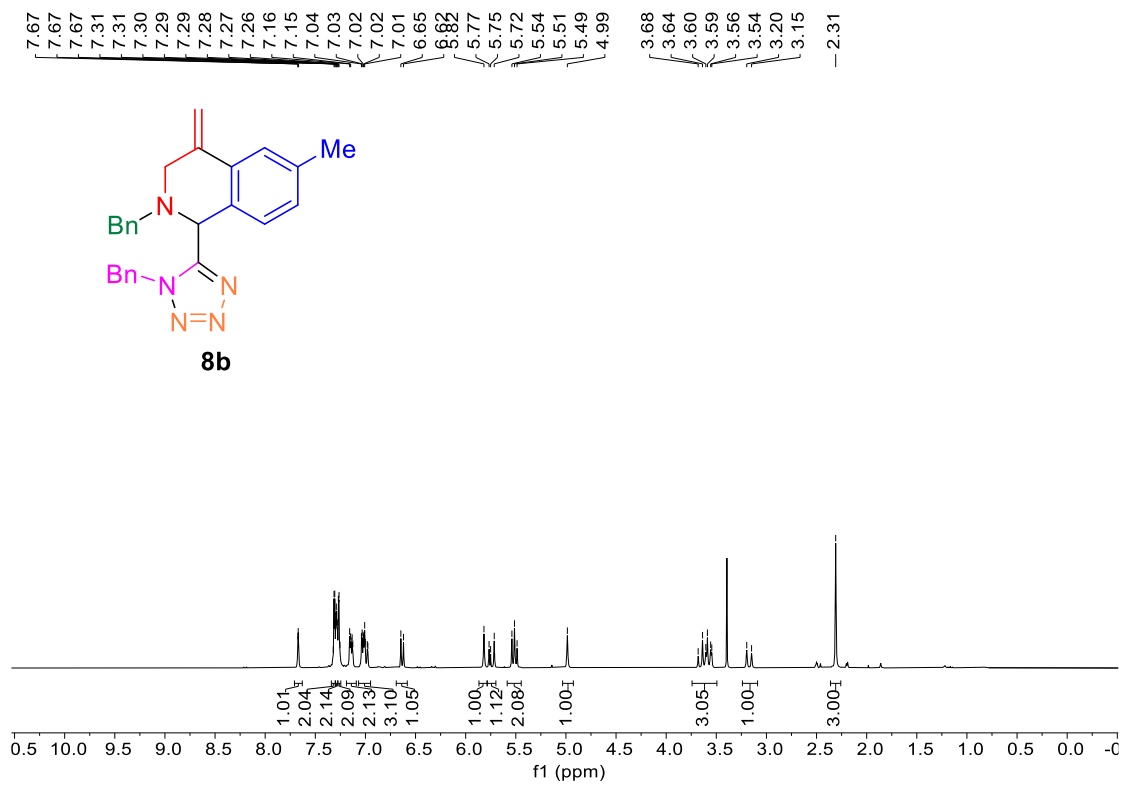


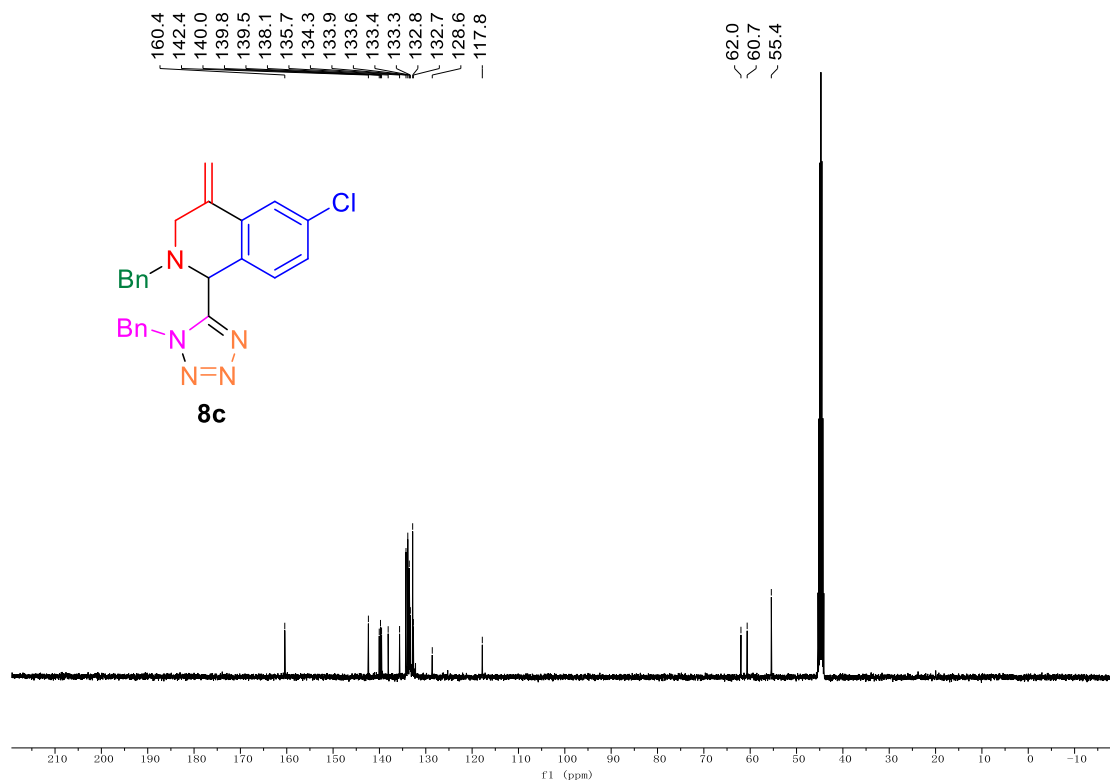
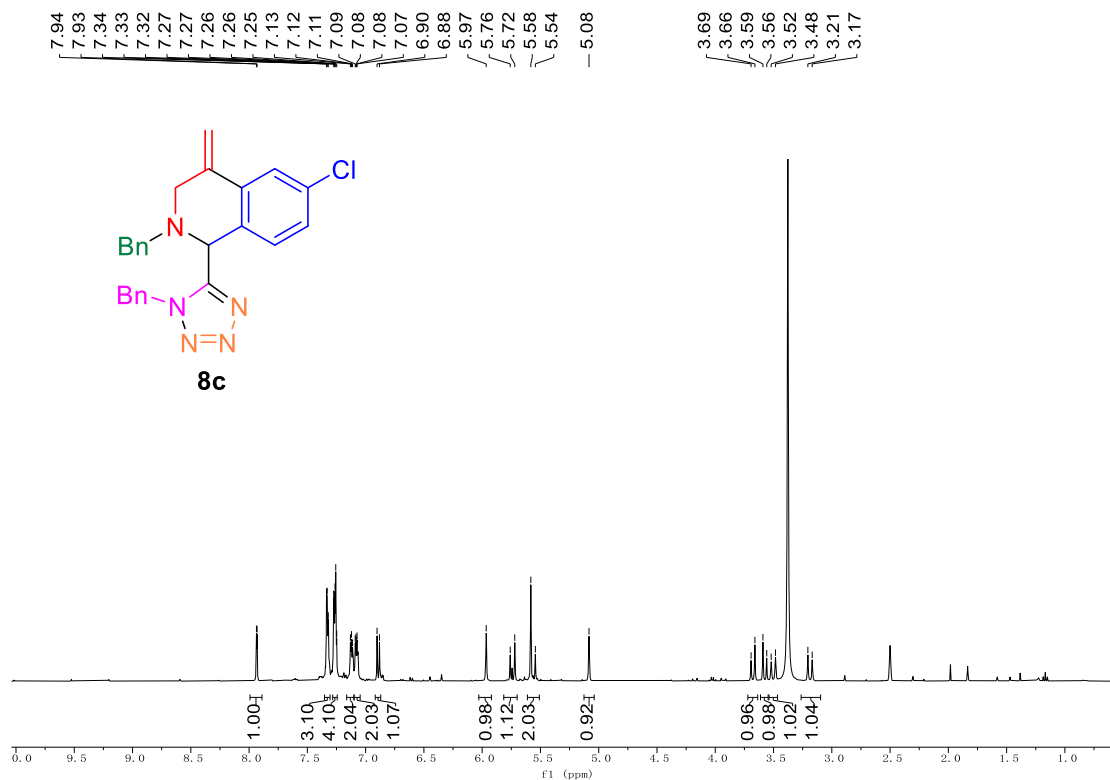


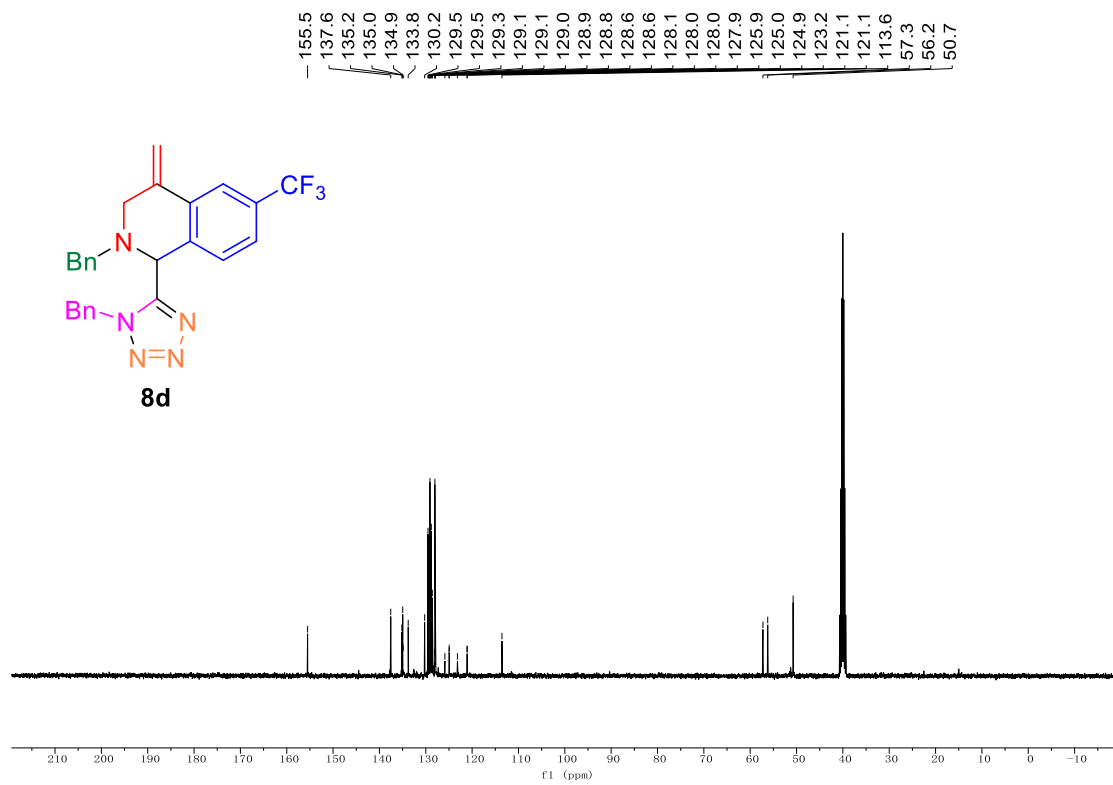
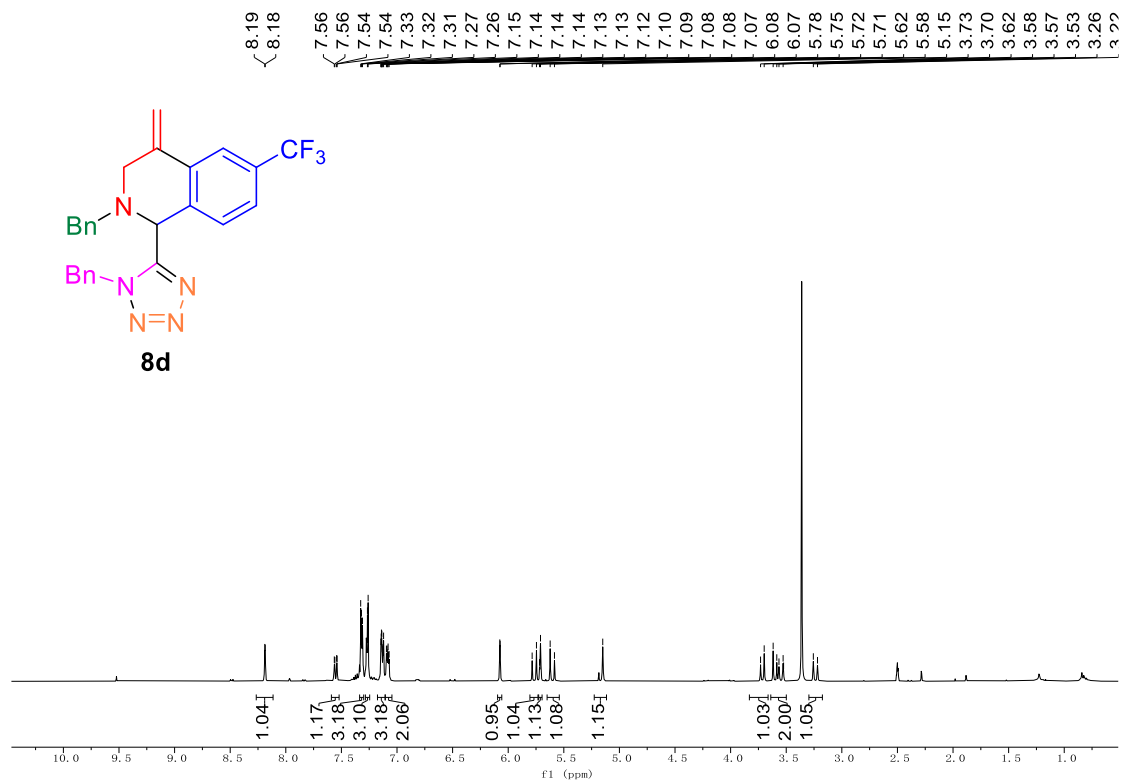


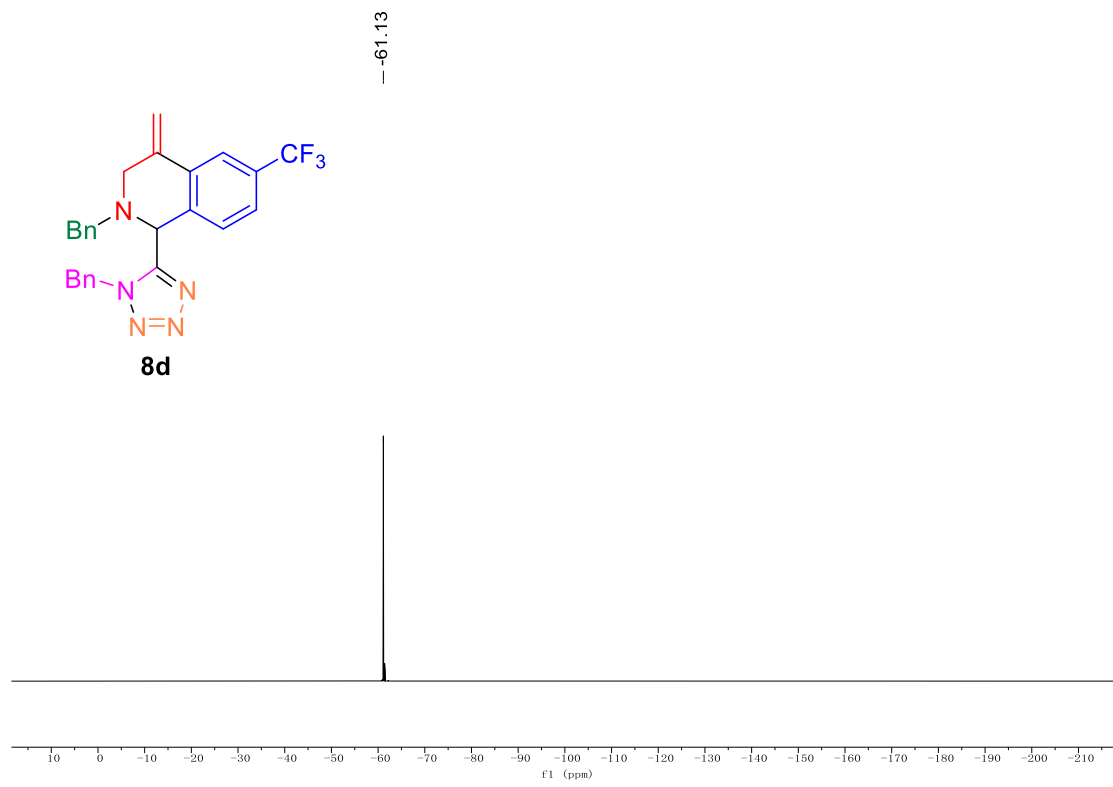


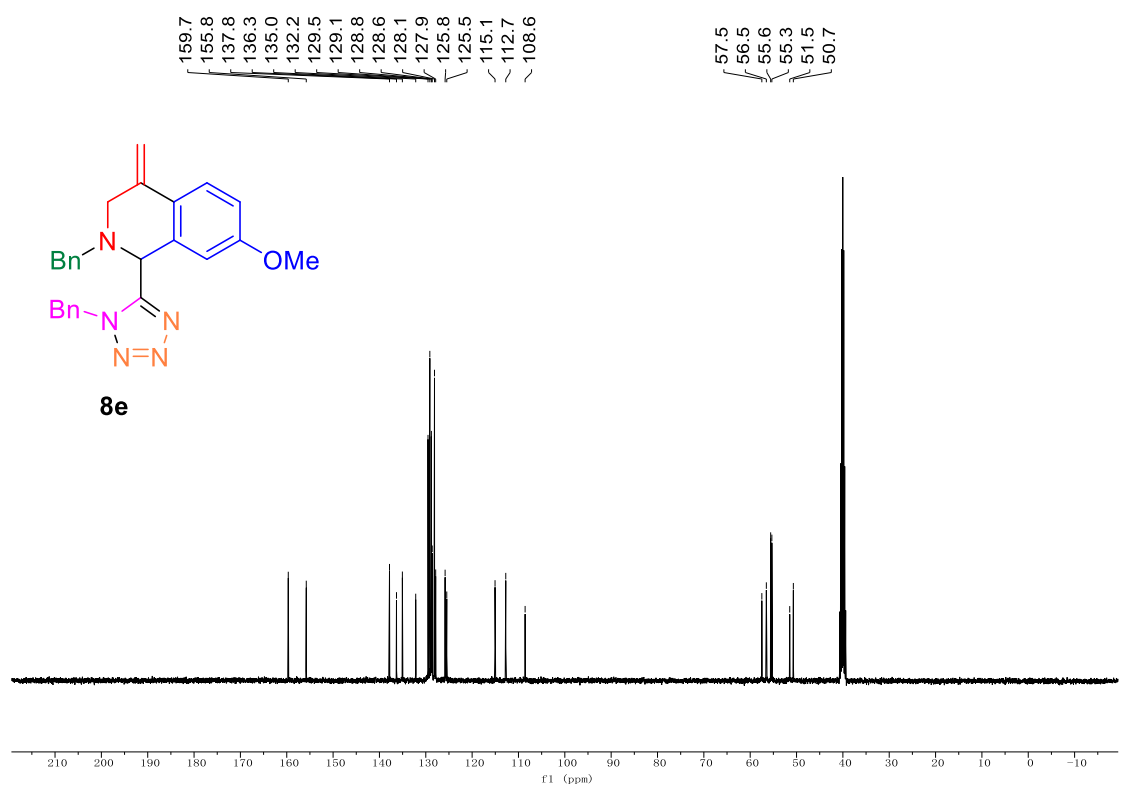
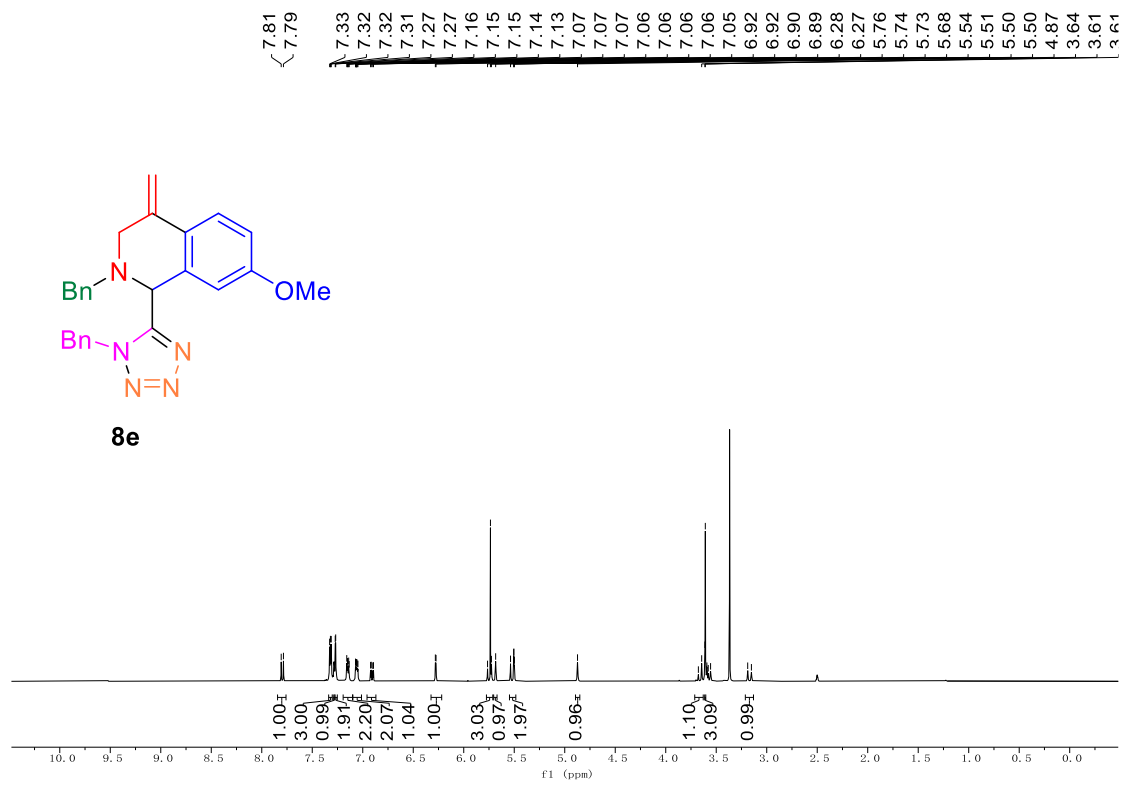




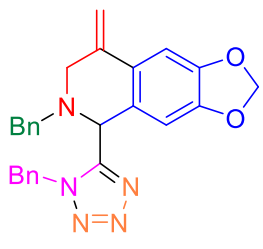




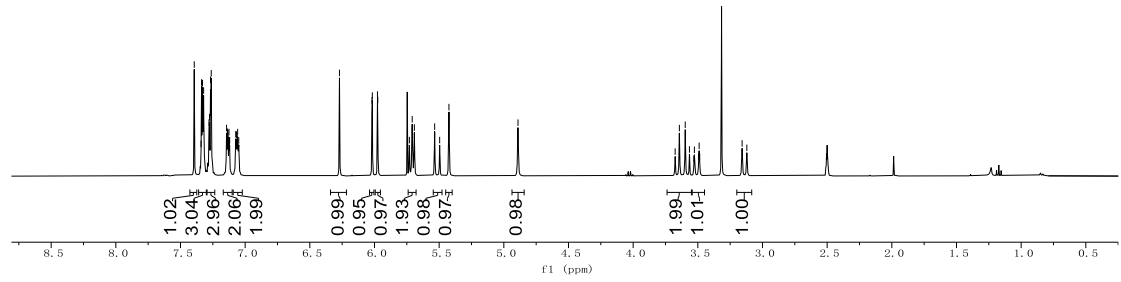




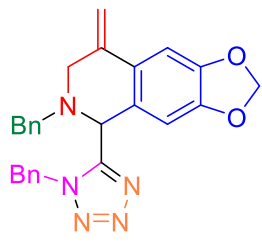
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